

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 76582

Name: Fenoldopam Mesylate Injection, 10 mg (base)/mL

Sponsor: West-Ward Pharmaceuticals International Limited
(formerly Bedford Laboratories)

Approval Date: October 12, 2004

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APPLICATION NUMBER:
ANDA 76582

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76582

APPROVAL LETTER

ANDA 76-582

OCT 12 2004

Bedford Laboratories
Attention: Molly L. Rapp
300 Northfield Road
Bedford, OH 44146

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 18, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fenoldopam Mesylate Injection USP, 10 mg (base)/mL, packaged in 10 mg (base)/1 mL and 20 mg (base)/2 mL single-dose vials.

Reference is also made to the Approvable letter issued by this office on April 20, 2004, and to your amendments dated July 9, July 27, and August 12, 2004.

The listed drug (RLD) referenced in your application, Corlopam Injection of Hospira Laboratories (Hospira), is subject to a period of exclusivity. As noted in the Agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", Hospira's exclusivity with respect to pediatric labeling providing for the use of Corlopam Injection in a pediatric population, (I-422), is scheduled to expire on April 1, 2007. Section 11 of the Best Pharmaceuticals for Children Act (BPCA), signed into law in January 2002, allows certain portions of Hospira's labeling which is the subject of pediatric exclusivity protection to be omitted from the labeling of products approved under Section 505(j) of the Act. The BPCA also permits the addition of language to the labeling of products approved under Section 505(j) that informs health care practitioners that Hospira's drug product has been approved for pediatric use. The Agency has determined that the final printed labeling you have submitted is in compliance with the BPCA with respect to pediatric use protected by exclusivity.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Fenoldopam Mesylate Injection USP, 10 mg (base)/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Corlopam[®] Injection, 10 mg (base)/mL, of Hospira Laboratories).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

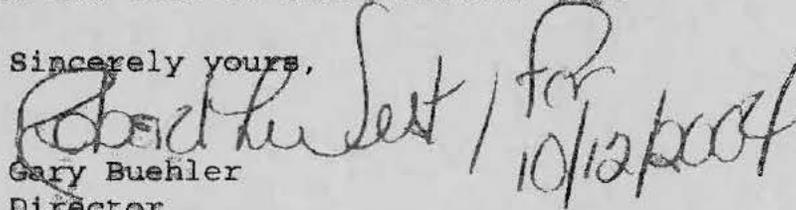
Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications,
HFD-42
5600 Fishers Lane
Rockville, MD 20857

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,


Gary Buehler

Director

Office of Generic Drugs

Center for Drug Evaluation and Research

cc: ANDA 76-582
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-600/Orange Book Staff

Endorsements:

HFD-623/B.Cai

HFD-623/S.Liu

HFD-617/W. Pamphile

HFD-613/J.Barlow

HFD-613/J.Grace

AL 10/7/04
S. H. Liu 10/8/04
Chad R 10/8/04
Jan 10/6/04

F/T by wp 8/26/04

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APPROVAL

AP
10/12/04
Robert West
10/12/2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76582

LABELING

0725

FENOLDOPAM
MESYLATE INJECTION USP

10 mg/mL

DILUTE PRIOR TO IV INFUSION
Rx ONLY

NDC 55385-071-01
1 mL Single-Dose Vial
Discard unused portion.
Manufactured for:
Baylor Laboratories[®]
Baylor, OH 44148

FIP-V01

MOVED
JUN 12 2004

FENOLDOPAM
MESYLATE INJECTION USP

10 mg/mL

DILUTE PRIOR TO IV INFUSION
Rx ONLY

NDC 55385-071-01
1 mL Single-Dose Vial
Discard unused portion.
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Discard unused portion.
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Baylor Laboratories[®]
Baylor, OH 44148

FIP-V01

MOVED
JUN 12 2004

FENOLDOPAM
MESYLATE INJECTION USP

20 mg/2 mL

(10 mg/mL)

DILUTE PRIOR TO IV INFUSION
Rx ONLY

NDC 5839-072-01
2 mL Single-Dose Vial
Clear and colorless to light
yellowish colorless
Manufactured for:
Baxter Laboratories
Buckeye, OH 44146

FDP-VAD1

APPROVED
OCT 12 2004

FENOLDOPAM
MESYLATE INJECTION USP

20 mg/2 mL

(10 mg/mL)

DILUTE PRIOR TO IV INFUSION
Rx ONLY

NDC 5839-072-01
2 mL Single-Dose Vial
Clear and colorless to light
yellowish colorless
Manufactured for:
Baxter Laboratories
Buckeye, OH 44146

FDP-VAD1

APPROVED
OCT 12 2004

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MESYLATE INJECTION USP

20 mg/2 mL

(10 mg/mL)

DILUTE PRIOR TO IV INFUSION
Rx ONLY

NDC 5839-072-01
2 mL Single-Dose Vial
Clear and colorless to light
yellowish colorless
Manufactured for:
Baxter Laboratories
Buckeye, OH 44146

FDP-VAD1

APPROVED
OCT 12 2004

FENOLDOPAM
MESYLATE INJECTION USP

20 mg/2 mL

(10 mg/mL)

DILUTE PRIOR TO IV INFUSION
Rx ONLY

NDC 5839-072-01
2 mL Single-Dose Vial
Clear and colorless to light
yellowish colorless
Manufactured for:
Baxter Laboratories
Buckeye, OH 44146

FDP-VAD1

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OCT 12 2004

FDP-C01

LOT
EXP

55390-071-01



**DILUTE PRIOR TO
IV INFUSION
Rx ONLY**

10 mg/mL

**FENOLDOPAM
MESYLATE INJECTION USP**

NDC 55390-071-01
1 mL Single-Dose Vial

Store at 2° to 30°C.
Discard unused portion.

Warning: Dilute before
administering. Inspect
visually for particulate
matter.

Usual Dosage: See
package insert.

10 mg/mL

**FENOLDOPAM
MESYLATE INJECTION USP**

NDC 55390-071-01
1 mL Single-Dose Vial

**FENOLDOPAM
MESYLATE INJECTION USP**

10 mg/mL

**DILUTE PRIOR TO
IV INFUSION**

Rx ONLY



Each mL contains, in
aqueous solution,
fenoldopam mesylate
equivalent to fenoldopam
10 mg; sodium metabisul-
fite 1 mg; citric acid
3.44 mg; sodium citrate
0.61 mg; propylene glycol
518 mg; pH range of
2.8 to 3.8.

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

Manufactured by:
Ben Venue Labs, Inc.
Bedford, OH 44146

12 2004
ROVED

NDC 55390-071-01
1 mL Single-Dose Vial

Usual Dosage: See
package insert.

FENOLDOPAM
MESYLATE INJECTION USP

Warning: Dilute before
administering. Inspect
visually for particulate
matter.

10 mg/mL

Store at 2° to 30°C.
Discard unused portion.

**DILUTE PRIOR TO
IV INFUSION**

Rx ONLY



LOT
EXP

FDP-C01

NDC 55390-071-01
1 mL Single-Dose Vial

Usual Dosage: See
package insert.

FENOLDOPAM
MESYLATE INJECTION USP

Warning: Dilute before
administering. Inspect
visually for particulate
matter.

10 mg/mL

Store at 2° to 30°C.
Discard unused portion.

**DILUTE PRIOR TO
IV INFUSION**

Rx ONLY



LOT
EXP

FDP-C01

NDC 55390-072-01
2 mL Single-Dose Vial

FENOLDOPAM
MESYLATE INJECTION USP

20 mg/2 mL

(10 mg/mL)
DILUTE PRIOR TO
IV INFUSION
Rx ONLY



LOT
EXP

FDP-CA01

Usual Dosage: See
package insert.

Warning: Dilute before
administering. Inspect
visually for particulate
matter.

Store at 2° to 30°C.
Discard unused portion.

(10 mg/mL)
20 mg/2 mL

MESYLATE INJECTION USP
FENOLDOPAM

NDC 55390-072-01
2 mL Single-Dose Vial

FENOLDOPAM
MESYLATE INJECTION USP

20 mg/2 mL

(10 mg/mL)
DILUTE PRIOR TO
IV INFUSION
Rx ONLY



APPROVED

Each mL contains, in
aqueous solution,
fenoldopam mesylate
equivalent to fenoldopam
10 mg; sodium metabisul-
fite 1 mg; citric acid
3.44 mg; sodium citrate
0.61 mg; propylene glycol
518 mg; pH range of
2.8 to 3.8.

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

Manufactured by:
Ben Venue Labs, Inc.
Bedford, OH 44146

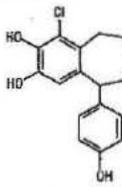
APPROVED

02/12/2004

FENOLDOPAM MESYLATE INJECTION USP

Rx ONLY

DESCRIPTION
Fenoldopam Mesylate Injection USP is a dopamine D₁-like receptor agonist. The product is formulated as a solution to be diluted for intravenous infusion. Chemically it is 6-chloro-2,3,4,5-tetrahydro-1-(p-hydroxy-phenyl)-1H-quinazolin-7(2H)-one methanesulfonate (salt) with the following structure:



APPROVED
OCT 12 2004

Fenoldopam mesylate is a white to off-white powder with a molecular weight of 401.87 and a molecular formula of C₁₇H₁₄ClN₂O₃S. It is sparingly soluble in water, ethanol and methanol, and is soluble in propylene glycol.

Each mL contains, in sterile aqueous solution, citric acid 3.44 mg; fenoldopam mesylate equivalent to fenoldopam 10 mg; propylene glycol 51.6 mg; sodium citrate dihydrate 0.61 mg; sodium metabisulfite 1 mg. The pH range is 2.8 to 3.8.

CLINICAL PHARMACOLOGY

Mechanism of Action: Fenoldopam is a rapid-acting vasodilator. It is an agonist for D₁-like dopamine receptors and binds with moderate affinity to α₁-adrenoceptors. It has no significant affinity for D₂-like receptors, α₂ and β adrenoceptors, 5HT₁ and 5HT₂ receptors, or muscarinic receptors. Fenoldopam is a selective inhibitor with the R-isomer responsible for the biological activity. The R-isomer has approximately 250-fold higher affinity for D₁-like receptors than does the S-isomer. In non-clinical studies, fenoldopam had no agonist effect on presynaptic D₁-like dopamine receptors, or α- or β-adrenoceptors, nor did it affect angiotensin-converting enzyme activity. Fenoldopam may increase norepinephrine plasma concentration.

In animals, fenoldopam has vasodilating effects in coronary, renal, mesenteric and peripheral arteries. All vascular beds, however, do not respond uniformly to fenoldopam. Vasodilating effects have been demonstrated in renal afferent and efferent arterioles.

Pharmacokinetics

Adult Patients: Fenoldopam, administered as a constant infusion at dosages of 0.01 to 1.0 mcg/kg/min, produced steady-state plasma concentrations that were proportional to infusion rates. The elimination half-life was about 5 minutes in mild to moderate hypertensives, with little difference between the R (active) and S isomers. Steady state concentrations are attained in about 20 minutes (4 half-lives). The steady state plasma concentrations of fenoldopam, at comparable infusion rates, were similar in normotensive subjects and in patients with mild to moderate hypertension or hypertensive emergencies.

The pharmacokinetics of fenoldopam were not influenced by age, gender, or race in adult patients with a hypertensive emergency. There have been no formal drug-drug interaction studies using intravenous fenoldopam. Clearance of parent (active) fenoldopam is not altered in adult patients with end-stage renal disease on continuous ambulatory peritoneal dialysis (CAPD) and is not altered in adult patients with severe hepatic failure. The effects of hemodialysis on the pharmacokinetics of fenoldopam have not been evaluated.

Pediatric Patients: Information related to the pharmacokinetics of fenoldopam injection in pediatric patients is approved for Abbott Laboratories' fenoldopam drug products. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled for pediatric use.

In radiolabeled studies in rats, no more than 0.005% of fenoldopam crossed the blood-brain barrier.

Excretion and Metabolism

Radiolabeled studies show that about 80% of infused fenoldopam is eliminated in urine, 10% in feces. Elimination is largely by conjugation, without participation of cytochrome P-450 enzymes. The principal routes of conjugation are methylation, glucuronidation, and sulfation. Only 4% of the administered dose is excreted unchanged. Animal data indicate that the metabolites are inactive.

Pharmacodynamics and Clinical Studies

Adult Patients: In a randomized, double-blind, placebo-controlled, 6-group study in 32 patients with mild to moderate essential hypertension (diastolic blood pressure between 95 and 110 mm Hg), and a mean baseline pressure of about 154/88 mm Hg, and heart rate of about 75 bpm, fixed-rate IV infusions of fenoldopam mesylate produced dose-related reductions in systolic and diastolic blood pressure. Infusions were maintained at a fixed rate for 48 hours. Table 1 shows the results of the study. The onset of response was rapid at all infusion rates, with the 10-minute response representing 90 to 100% of the one-hour response in all groups. There was a dose-dependent partial tolerance at 48 hours in the two higher dose infusions, but a substantial effect persisted through 48 hours. When infusions were stopped, blood pressure gradually returned to pretreatment values with no evidence of rebound. This study suggests that there is no greater response to 0.6 mcg/kg/min than to 0.4 mcg/kg/min.

Table 1
PHARMACODYNAMIC EFFECTS OF FENOLDOPAM IN MILD TO MODERATE ADULT HYPERTENSIVE PATIENTS

Time Point and Mean Change From Time Zero ± SE	Drug Dosage (mcg/kg/min)				
	Placebo n=7	0.04 n=7	0.1 n=7	0.4 n=5	0.6 n=5
10 Minutes of Infusion*					
Systolic BP	0±0	-15±8	-19±8	-14±4	-24±6
Diastolic BP	0±2	-5±3	-12±4	-15±3	-20±4
Heart rate	+2±2	+5±2	+5±1	+15±3	+19±2
30 Minutes of Infusion*					
Systolic BP	-0±5	-17±6	-18±6	-14±8	-26±6
Diastolic BP	-0±3	-7±3	-16±4	-14±3	-20±2
Heart rate	+2±2	+3±2	+10±2	+18±3	+23±3
1 Hour of Infusion*					
Systolic BP	-15±4	-22±7	-22±7	-26±9	-22±6
Diastolic BP	-5±3	-9±2	-18±4	-19±4	-21±1
Heart rate	+1±3	+5±2	+12±3	+19±4	+25±4
4 Hours of Infusion*					
Systolic BP	-14±5	-16±9	-31±10	-23±11	-25±7
Diastolic BP	-14±5	-9±4	-18±9	-25±3	-23±1
Heart rate	+5±3	+6±3	+10±4	+21±3	+27±7
24 Hours of Infusion*					
Systolic BP	-22±5	-23±8	-35±7	-25±6	-28±11
Diastolic BP	-11±5	-11±5	-23±10	-22±5	-15±5
Heart rate	+6±3	+5±3	+13±2	+17±4	+15±3
48 Hours of Infusion*					
Systolic BP	-12±5	-21±6	-22±8	-9±5	-14±10
Diastolic BP	-5±5	-10±6	-9±7	9±2	-3±3
Heart rate	+1±2	0±4	+1±4	+12±3	+6±3

*Mean change from time zero ± SE

In a multicenter, randomized, double-blind comparison of four infusion rates, fenoldopam mesylate was administered as constant rate infusions of 0.01, 0.03, 0.1 and 0.2 mcg/kg/min for up to 24 hours to 94 adult patients experiencing hypertensive emergencies (diastolic blood pressure ≥120 mm Hg with evidence of compromise of end-organ function involving the cardiovascular, renal, cerebral or ocular systems). Infusion rates could be doubled after one hour if clinically indicated. There were dose-related, rapid-onset, decreases in systolic and diastolic blood pressure and increases in heart rate (Table 2).

Table 2
PHARMACODYNAMIC EFFECTS OF FENOLDOPAM IN ADULT HYPERTENSIVE EMERGENCY PATIENTS

Time Point and Parameter	Drug Dosage (mcg/kg/min)			
	0.01 n=25	0.03 n=24	0.1 n=22	0.2 n=23
Pre-infusion Baseline				
Systolic BP-mmHg	210±21	206±20	205±24	211±17
Diastolic BP-mmHg	136±15	135±11	133±14	136±15
Heart rate-minutes	87±20	84±14	81±19	80±14
15 Minutes of Infusion*				
Systolic BP	-5±4	-7±4	-16±4	-19±4
Diastolic BP	-5±3	-6±3	-12±2	-17±2
Heart rate	-2±3	+1±1	+2±1	+17±2
30 Minutes of Infusion*				
Systolic BP	-6±4	-11±4	-21±3	-19±4
Diastolic BP	-10±3	-12±3	-17±3	-20±2
Heart rate	-2±3	-1±1	+3±2	+17±3
1 Hour of Infusion*				
Systolic BP	-6±3	-8±4	-19±4	-20±4
Diastolic BP	-6±3	-13±3	-18±2	-20±2
Heart rate	-1±3	0±2	+3±2	+17±3
4 Hours of Infusion*				
Systolic BP	-14±4	-20±5	-23±4	-27±4
Diastolic BP	-12±3	-18±3	-21±3	-23±3
Heart rate	2±4	0±2	4±2	+17±2

*Mean change from baseline ± SE

Two hundred and thirty six severely hypertensive adult patients (DBP ≥120 mm Hg), with or without end-organ compromise, were randomized to receive two open-label studies either fenoldopam or nitroglycerin. The response rate was 79% (52/17) in the fenoldopam group and 77% (50/18) in the nitroglycerin group. Response required a decline in systolic diastolic blood pressure to less than 110 mm Hg if the baseline were between 120 and 150 mm Hg, inclusive, or by 20 mm Hg if the baseline were ≥160 mm Hg. Patients were titrated to the desired effect. For fenoldopam, the dose ranged from 0.1 to 1.5 mcg/kg/min; for nitroglycerin, the dose ranged from 1.0 to 8.0 mcg/kg/min. As in the study in mild to moderate hypertension, most of the effect seen at one hour is present at 15 minutes. The additional effect seen after 1 hour occurs in all groups and may not be drug-related (there was no placebo group for evaluation).

Pediatric Patients: Information related to the pharmacokinetics of fenoldopam injection in pediatric patients is approved for Abbott Laboratories' fenoldopam drug products. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled for pediatric use.

INDICATIONS AND USAGE

Adult Patients: Fenoldopam is indicated for the in-hospital, short-term (up to 48 hours) management of severe hypertension when rapid, but quickly reversible, emergency reduction of blood pressure is clinically indicated, including malignant hypertension with cardiovascular and organ function. Transition to oral therapy with another agent on hospital admission after blood pressure is stable during fenoldopam mesylate infusion.

Pediatric Patients: Information related to the indicated use of fenoldopam injection in pediatric patients is approved for Abbott Laboratories' fenoldopam drug products. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled for pediatric use.

CONTRAINDICATIONS

None known.

WARNINGS

Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

Intraocular Pressure: In a clinical study of 12 patients with open-angle glaucoma or ocular hypertension (mean baseline intraocular pressure was 23.2 mm Hg with a range of 22 to 33 mm Hg), infusion of fenoldopam mesylate at escalating doses ranging from 0.05 to 0.5 mcg/kg/min over a 3.5 hour period caused a dose-dependent increase in intraocular pressure (IOP). At the peak effect, the intraocular pressure was raised by a mean of 6.5 mm Hg (range -2 to +8.5 mm Hg, corrected for placebo effect). Upon discontinuation of the fenoldopam mesylate infusion, the IOP returned to baseline values within 2 hours. Fenoldopam mesylate administration to patients with glaucoma or ocular hypertension should be undertaken with caution.

Thyroidism: Fenoldopam mesylate causes a dose-related tachycardia (Table 2), particularly with infusion rates above 0.1 mcg/kg/min. Tachycardia in adults disappears over time but remains substantial at higher doses. Tachycardia in pediatric patients at doses > 0.5 mcg/kg/min persists at least for 4 hours.

Hypotension: Fenoldopam mesylate may occasionally produce symptomatic hypotension and cause monitoring of blood pressure during administration is essential. (See ADVERSE REACTIONS.) It is particularly important to avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage. In pediatric patients, fenoldopam mesylate was only administered to patients with an intraventricular catheter.

Hypokalemia: Decreases in serum potassium occasionally to values below 3 mEq/L were observed after less than 6 hours of fenoldopam infusion. It is not clear if the hypokalemia reflects a pressure-related effect with enhanced potassium-sodium exchange or a direct drug effect. During clinical trials, electrolytes were monitored at intervals of 6 hours. Hypokalemia was treated with either oral or intravenous potassium supplementation. Patient management should include appropriate attention to serum electrolytes.

Intraocular Pressure: The effect of fenoldopam in the presence of increased intraocular pressure has not been studied.

Drug Interactions with Beta-Blockers: Concomitant use of fenoldopam with beta-blockers should be avoided. If the drugs are used together, caution should be exercised because unexpected hypotension could result from beta-blocker inhibition of the sympathetic reflex response to fenoldopam.

Drug Interactions, General: Although there have been no formal interaction studies, intravenous fenoldopam mesylate has been administered safely with drugs such as diuretics and sublingual nitroglycerin. There is limited experience with concomitant anti-hypertensive agents such as alpha-blockers, calcium channel-blockers, ACE inhibitors, and diuretics (both thiazide-like and loop).

Contraception, Pregnancy, Lactation and Fertility: In a 24-month study, mice treated orally with fenoldopam at 12.5, 25, or 50 mcg/kg/day, reduced to 75 mcg/kg/day on day 230 of study showed no increase above controls in the incidence of neoplasms. Female mice in the highest dose group had an increased incidence and degree of severity of a fibrous eosinophilic lesion of the stomach compared with control or low dose animals. Compared to controls, female mice in the middle- and upper-dose groups had a higher incidence and degree of severity of chronic nephritis. These pathologic lesions were not seen in male mice treated with fenoldopam.

In a 24-month study, rats treated orally with fenoldopam at 5, 10 or 20 mcg/kg/day, with the mid- and high-dose groups increased to 15 or 25 mcg/kg/day, respectively, on day 372 of the study, showed no increase above controls in the incidence or type of neoplasms. Compared with the controls, rats in the mid- and high-dose groups had a higher incidence of hyperplasia of collicular duct epithelium at the tip of the nasal cavity.

Fenoldopam did not induce bacterial gene mutation in the Ames test or mammalian gene mutation in the Chinese hamster ovary (CHO) cell assay. In the *in vitro* chromosomal aberration assay with CHO cells, fenoldopam was associated with statistically significant and dose-dependent increases in chromosomal aberrations, and in the proportion of aberrant metaphases. However, no chromosomal damage was seen in the *in vivo* mouse micronucleus or bone marrow assays.



Oral fertility and general reproduction performance studies in male and female rats at 12.5, 37.5 or 75 mg/kg/day revealed no impairment of fertility or reproduction performance due to fenoldopam.

Pregnancy: Teratogenic Effects; Pregnancy Category B. Oral reproduction studies have been performed in rats and rabbits at doses of 12.5 to 200 mg/kg/day and 6.25 to 25 mg/kg/day, respectively. Studies have revealed maternal toxicity at the highest doses tested but no evidence of impaired fertility or harm to the fetus due to fenoldopam. However, there are no adequate and well-controlled studies in pregnant women. Since animal reproduction studies are not always predictive of human response, fenoldopam should be used in pregnancy only if clearly needed.

Nursing Mothers: Fenoldopam is excreted in milk in rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when fenoldopam is administered to a nursing woman.

Pediatric Use: Clinical study information related to the safety and effectiveness of fenoldopam injection in pediatric patients aged < 1 month to 12 years old is approved for Abbott Laboratories' fenoldopam drug product. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled for pediatric use.

Geriatric Use: Clinical studies of fenoldopam did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adult Patients: Fenoldopam mesylate causes a dose-related fall in blood pressure and increase in heart rate (see PRECAUTIONS, Tachycardia, and Hypotension). In controlled clinical studies of severe hypertension in patients with end-organ damage, 9% (4/17) of patients with new evidence of excessive falls in blood pressure, increased heart rate, or other signs of ischemic cardiac events or worsened heart failure, although these events have not been observed. The most common events reported as associated with fenoldopam mesylate use are headache, cutaneous dilation (flushing), nausea, and hypotension, each reported in more than 25% of patients.

Adverse reactions in controlled trials in hypertension adult patients

Adverse events occurring more than once in any dosing group (or in a potentially important or possibly drug-related) in the fixed-dose controlled infusion studies are presented in the following table by infusion-rate group. There was no clear dose relationship, except possibly for headache, nausea, flushing.

Table 3
ADVERSE EVENTS* FROM FIXED-DOSE INFUSION STUDIES BY DOSAGE GROUP

Body System	Event	Fenoldopam Mesylate Dosage (mg/kg/min) (Adults)					
		Placebo (n=7)	0.01 (n=6)	0.03-0.04 (n=31)	0.1 (n=26)	0.3-0.4 (n=29)	0.8-0.9 (n=11)
Body/Geriatric	Headache	1	5	4	7	8	6
	Injection site reaction	0	1	3	8	3	2
	ST-T abnormalities (primarily T-wave inversion)	0	2	4	0	1	0
Cardiovascular	Flushing	0	0	0	0	1	5
	Hypotension**	0	0	0	2	0	2
	Postural hypotension	0	2	3	0	0	0
	Tachycardia**	0	0	0	0	0	2
Digestive	Nausea	0	3	0	3	5	4
	Vomiting	0	2	0	2	1	2
	Abdominal pain/flatulence	0	2	0	0	2	1
	Constipation	0	0	0	0	0	2
Metabolic and Nutritional	Diarrhea	0	0	0	0	2	3
	Increased aspartate**	0	0	2	0	0	0
Nervous	Hypokalemia**	0	2	2	0	1	0
	Nervousness/tachycardia	0	0	1	0	0	2
Respiratory	asthenia	0	2	0	0	0	0
	Dyspnea	0	1	1	2	2	0
	Nasal congestion	0	0	0	0	0	2
Skin and Appendages	Swelling	0	0	0	1	1	2
	Urinary tract infection	0	2	0	1	0	0
Musculoskeletal	Back pain	0	1	0	1	2	2

*Includes events reported by 2 or more patients receiving fenoldopam mesylate treatment across all dose groups.
**Investigator defined; no protocol definition.

Adverse events in overall database

The adverse event incidences listed below are based on observations of over 1,200 fenoldopam mesylate treated adult patients and are listed in the Table 3 above.

Events reported with a frequency between 0.5 to 5% in patients treated with IV fenoldopam mesylate

Cardiovascular:	arrhythmias, palpitations, bradycardia, heart failure, ischemic heart disease, myocardial infarction, angina pectoris
Abnormalities:	elevated BUN, elevated serum glucose, elevated transaminase, elevated LDH
General Body:	non-specific chest pain, pyrexia
Hematology/Lymphatics:	leukocytosis, bleeding
Respiratory:	dyspnea, upper respiratory disorder
Genitourinary:	oliguria
Musculoskeletal:	limb cramp

Pediatric Patients: Information relating to treatment-emergent adverse events of fenoldopam injection in pediatric patients is approved for Abbott Laboratories' fenoldopam drug product. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled for pediatric use.

ANIMAL TOXICOLOGY

Unusual histologic findings (arterial lesions in the rat) with fenoldopam are summarized below. These findings have not been observed in mice or dogs. No evidence of a similar lesion in humans has been observed.

Arterial lesions characterized by medial necrosis and hemorrhage have been seen in renal and splanchnic arteries of rats given fenoldopam mesylate by continuous intravenous infusion at doses of 1 to 100 mg/kg/day for 24 hours. The incidence of these lesions is dose related. Arterial lesions morphologically identical to those observed with fenoldopam have been reported in rats infused with doxamine. Data suggest that the mechanism for this injury involves activation of D₁-like dopaminergic receptors. Such lesions have not been seen in dogs given doses up to 100 mg/kg/day by continuous intravenous infusion for 24 hours, nor were they seen in dogs infused at the same dose for 8 hours daily for 24 days. The clinical significance of this finding is not known.

Oral administration of fenoldopam doses of 10 to 15 mg/kg/day or 20 to 25 mg/kg/day to rats for 24 months induced a higher incidence of polycystic nodules compared to controls. Such lesions were not seen in rats given 5 mg/kg/day of fenoldopam or in mice given the drug at doses up to 50 mg/kg/day for 24 months.

OVERDOSE

Intentional fenoldopam mesylate overdosage has not been reported. The most likely reaction would be excessive hypotension which should be treated with drug discontinuation and appropriate supportive measures.

DOSAGE AND ADMINISTRATION

Adult Patients: The optimal magnitude and rate of blood pressure reduction in severely hypertensive patients have not been rigorously determined, but, in general, both daily and too rapid decreases appear undesirable in sick patients. An initial fenoldopam mesylate injection dose may be chosen from Tables 1 and 2 in the CLINICAL PHARMACOLOGY section that produces the desired magnitude and rate of blood pressure reduction in a given clinical situation. Doses below 0.1 mg/kg/min have very

modest effects and appear only marginally useful in this population. In general, as the initial dose increases, there is a greater and more rapid blood pressure reduction. However, lower initial doses (0.03 to 0.1 mg/kg/min) titrated slowly have been associated with less reflex tachycardia than have higher initial doses (20.3 mg/kg/min). In clinical trials, doses from 0.01 to 1.8 mg/kg/min have been studied. Most of the effect of a given infusion rate is attained in 15 minutes.

Fenoldopam mesylate injection should be administered by continuous intravenous infusion. A bolus dose should not be used. Hypotension and rapid decreases of blood pressure should be avoided. The initial dose should be titrated upward or downward, no more frequently than every 15 minutes (and less frequently as goal pressure is approached) to achieve the desired therapeutic effect. The recommended increments for titration are 0.05 to 0.1 mg/kg/min.

Use of a calibrated, mechanical infusion pump is recommended for proper control of infusion rate during fenoldopam mesylate infusions. In clinical trials, fenoldopam mesylate injection treatment was safely performed without the need for intra-arterial blood pressure monitoring; blood pressure and heart rate were monitored at frequent intervals, typically every 15 minutes. Frequent blood pressure monitoring is recommended.

Fenoldopam mesylate injection infusion can be abruptly discontinued or gradually tapered prior to discontinuation. Oral antihypertensive agents can be added during fenoldopam mesylate injection infusion or following its discontinuation. Patients in controlled clinical trials have received intravenous fenoldopam mesylate injection for as long as 48 hours.

PREPARATION OF INFUSION SOLUTION

WARNING: CONTENTS OF VIALS MUST BE DILUTED BEFORE INFUSION. EACH VIAL IS FOR SINGLE USE ONLY.

Dilution:

Adult Patients: The fenoldopam mesylate injection vial concentrate must be diluted in 0.9% Sodium Chloride Injection or 5% Dextrose Injection using the following dilution schedule:

mL of Concentrate (mg of drug)	Added to	Final Concentration
4 mL (40 mg)	1000 mL	40 mcg/mL
2 mL (20 mg)	500 mL	40 mcg/mL
1 mL (10 mg)	250 mL	40 mcg/mL

The drug dose rate must be individualized according to body weight and according to the desired rapidly and extent of pharmacodynamic effect. Table 4 provides the calculated infusion volume in mL/hour for a range of drug doses and body weights. The infusion should be administered using a calibrated mechanical infuser pump that can accurately and reliably deliver the desired infusion rate.

Infusion Rates:

Table 4
FENOLDOPAM ADULT INFUSION RATES (mL/hour)

Body Weight (kg)	Infusion Rate				
	0.025 mg/kg/min	0.05 mg/kg/min	0.1 mg/kg/min	0.2 mg/kg/min	0.3 mg/kg/min
	Infusion Rate (mL/hour) of 40 mcg/mL solution				
40	1.5	3	6	12	18
50	1.5	3.6	7.5	15	22.5
60	2.3	4.5	9.0	18	27
70	2.6	5.3	10.5	21	31.5
80	3	6	12	24	36
90	3.4	6.8	13.5	27	40.5
100	3.8	7.5	15	30	45
110	4.1	8.3	16.5	33	49.5
120	4.5	9	18	36	54
130	4.9	9.8	19.5	39	58.5
140	5.3	10.5	21	42	63
150	5.6	11.3	22.5	45	67.5

Table 4 (continued)
FENOLDOPAM ADULT INFUSION RATES (mL/hour)

Body Weight (kg)	Infusion Rate				
	0.5 mg/kg/min	0.8 mg/kg/min	1 mg/kg/min	1.4 mg/kg/min	1.8 mg/kg/min
	Infusion Rate (mL/hour) of 40 mcg/mL solution				
40	30	48	60	84	90
50	37.5	60	75	105	120
60	45	72	90	126	144
70	52.5	84	105	147	165
80	60	96	120	168	180
90	67.5	108	135	189	210
100	75	120	150	210	240
110	82.5	132	165	231	254
120	90	144	180	252	280
130	97.5	156	195	273	312
140	105	168	210	294	336
150	112.5	180	225	315	360

The diluted solution is stable under normal ambient light and temperature conditions for at least 24 hours. Diluted solution that is not used within 24 hours of preparation should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter or discoloration is observed, the drug should be discarded.

Pediatric Patients: Information relating to the dosing and administration of fenoldopam injection in pediatric patients is approved for Abbott Laboratories' fenoldopam drug product. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled for pediatric use.

HOW SUPPLIED

Fenoldopam Mesylate Injection TRP is supplied in single-dose vials as follows:
NDC 50398-071-01, 10 mg/mL; 1 mL vial, individually boxed.
NDC 50398-072-01, 10 mg/mL; 2 mL vial, individually boxed.

Store at 2° to 30°C (35.0° to 86°F). Observe usual caution.

Manufactured by:
Seri Veng Laboratories, Inc.
Bedford, OH 44146

Manufactured for:
Zellari Laboratories™
Bedford, OH 44140

August 2004

FDP-P01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76582

LABELING REVIEWS

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-582
 Date of Submission: August 12, 2004
 Applicant's Name: Bedford Laboratories
 Established Name: Fenoldopam Mesylate Injection USP, 10 mg/mL

APPROVAL SUMMARY

1. Do you have 12 Final Printed Labels and Labeling? Yes

2. **CONTAINER – 1 mL and 2 mL single-dose vials**

Satisfactory in final print as of the August 12, 2004 submission
 (See blue jacket volume 3.1)

3. **CARTON**

Satisfactory in final print as of the August 12, 2004 submission.
 (See blue jacket volume 3.1)

4. **PACKAGE INSERT**

Satisfactory in final print as of the August 12, 2004 submission.
 (See blue jacket volume 3.1)

5. Revisions needed post-approval: None

6. **Patent Data:**

Patent Data – NDA 19-922

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
		None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 19-922

Code	Reference	Expiration	Labeling Impact
I-422	INDICATED FOR THE IN-HOSPITAL SHORT-TERM (UP TO 4 HOURS) REDUCTION IN BLOOD PRESSURE IN PEDIATRIC PATIENTS	4/1/07	Carved Out and substituted with Pediatric Division/New Drug Division and OGD recommended statements

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Corlopam® Injection

NDA Number: 19-922

NDA Drug Name: Corlopam® Injection

NDA Firm: Abbott Laboratories; N 19-922/SE-005; Approved April 1, 2004

Date of Approval of NDA Insert and supplement: Approved April 1, 2004; N 19-922/SE-005

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug, Corlopam® Injection.

***** **FIRST GENERIC** *****

FOR THE RECORD:

1. The labeling submitted by the firm was based on the most recently approved labeling for this drug product. Labeling was recently approved on April 1, 2004 for the RLD.

2. **Patent/ Exclusivities:**

Patent Data – NDA 19-922

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
		None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data- NDA 19-922

Code	Reference	Expiration	Labeling Impact
I-422	INDICATED FOR THE IN-HOSPITAL SHORT-TERM (UP TO 4 HOURS) REDUCTION IN BLOOD PRESSURE IN PEDIATRIC PATIENTS	4/1/07	Carved Out and substituted with Pediatric Division/New Drug Division and OGD recommended statements

3. Storage/Dispensing Conditions:

NDA: Store at 2° to 30°C.

ANDA: Store at 2° to 30°C. Discard unused portion

(b) (4)

4. Product Line:

The innovator markets their product in two ampule sizes. 1 mL and 2 mL ampules utilizing the concentration of 10mg/mL.

The applicant proposes to market their product in 1 mL and 2 mL vials utilizing the 10 mg/mL concentration as well.

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the **statement of components appearing on page 66, Vol. A. 1.1.**

6. Container/Closure(See page 0595 in Vol. A.. 1.2)

Containers: Type 1 glass container

Closure:BVL stopper with flip-off seal

7. All manufacturing will be done by Ben Venue Laboratories for Bedford Laboratories, Inc. (See pg. 00112 in vol. A. 1.1)

Date of Review: 8/25/04

Date of Submission: 8/12/04

Primary Reviewer: Jim Barlow

Date:

Team Leader: John Grace

Date:

cc:

ANDA: 76582

DUP/DIVISION FILE

HFD-613/JBarlow/JGrace (no cc)

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Review

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 76-582
Date of Submission: March 19, 2004
Applicant's Name: Bedford Laboratories
Established Name: Fenoldopam Mesylate Injection USP, 10 mg/mL

Labeling Deficiencies:

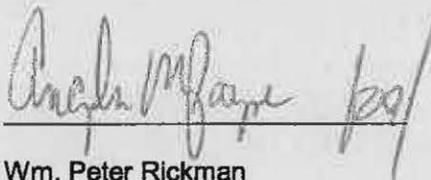
GENERAL COMMENTS -

On April 1, 2004, New Patient Population labeling was approved for the RLD, Corlopam® (NDA 19-922/SE-005). The Agency defers comments at this time, but will advise your firm of the new labeling language after further review.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference-listed drug. In order to keep your ANDA current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where Inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility Information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

***** FIRST GENERIC *****

FOR THE RECORD:

1. The labeling submitted by the firm was based on the most recently approved labeling for this drug product. Labeling was recently approved on April 1, 2004 for the RLD. The Agency will advise the firm at a later date.

2. Patent/ Exclusivities:

Patent Data – NDA 19-922

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
		None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 19-922

Code	Reference	Expiration	Labeling Impact
I-422	Pending in Orange Book (NPP information)	4/1/07	Carved Out

3. Storage/Dispensing Conditions:

NDA: Store at 2° to 30°C.

ANDA: Store at 2° to 30°C. Discard unused portion

(b) (4)

4. Product Line:

The innovator markets their product in two ampule sizes. 1 mL and 2 mL ampules utilizing the concentration of 10mg/mL.

The applicant proposes to market their product in 1 mL and 2 mL vials utilizing the 10 mg/mL concentration as well.

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the **statement of components appearing on page 66, Vol. A. 1.1.**

6. Container/Closure(See page 0595 in Vol. A. 1.2)

Containers: Type 1 glass container

Closure:BVL stopper with flip-off seal

7. All manufacturing will be done by Ben Venue Laboratories for Bedford Laboratories, Inc. (See pg. 00112 in vol. A. 1.1)

Date of Review: 4/21/04

Primary Reviewer: Jim Barlow

Date of Submission: 3/19/04

Date: 4/24/04

Team Leader: John Grace

Date:

cc:

ANDA: 76-582

DUP/DIVISION FILE

HFD-613/JBarlow/JGrace (no cc)

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Review

*John Grace 4/26/04
for Jim Grace.*

Please see listing of commitment (March 19, 2004) container/carton.

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 76-582
Date of Submission: December 18, 2002
Applicant's Name: Bedford Laboratories
Established Name: Fenoldopam Mesylate Injection USP, 10 mg/mL

Labeling Deficiencies:

1. CONTAINER – 1 mL and 2 mL single-dose vials

- a. Front Panel: Revise your expression of strength format to be the same as the RLD. The RLD has expressed the total drug contents and the concentration with the total drug contents in the color differentiation boxes as follows -

20 mg
(10 mg/mL)

AND

10mg
(10 mg/mL)

- b. Relocate the " Dilute before administration" statement directly beneath the expression of strength on the front panel of the label -

xxmg
(xx mg/mL)

DILUTE BEFORE ADMINISTRATION
Rx only

- c. Side panel; We encourage you to revise to read as follows -

xx mL single-dose vial

- d. Side panel; Please revise to include the statement "Discard unused portion" on your labels.

2. CARTON

- a. 10 mg/mL (1 mL vial); Front panel -

We encourage you to revise to read as follows -

1 mL single-dose vial

- b. 20 mg vial (2 mL vial); Front panel -

We encourage you to revise to read as follows -

2 mL single-dose vial

c. See comments 1.(a.) and 1.(d.) listed above for requested revisions.

3. PACKAGE INSERT

a. DESCRIPTION

Revise your molecular weight to read "401.87" to be in accord with the USP.

b. INDICATIONS AND USAGE

Fenoldopam mesylate injection...

c. PRECAUTIONS

Revise subsection title to read as follows – [Delete "Teratogenic Effects"]

Pregnancy: Pregnancy Category B.

d. DOSAGE AND ADMINISTRATION

i. Substitute "fenoldopam mesylate" throughout the text with "fenoldopam mesylate injection"

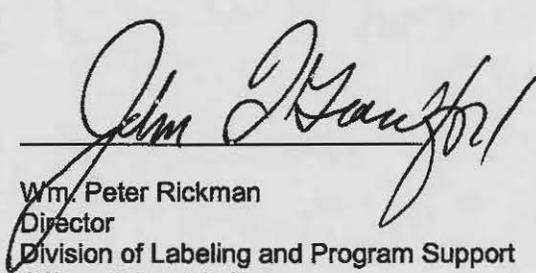
ii. Fifth paragraph; second sentence -

Oral antihypertensive agents can...

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP Item? If so, USP supplement in which verification was assured. USP 24	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the Inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from Inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in Inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility Information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

***** FIRST GENERIC *****

FOR THE RECORD:

1. The labeling submitted by the firm was based on the most recently approved labeling for this drug product. Labeling was recently approved on December 15, 1997 for the RLD.

2. Patent/ Exclusivities:

Patent Data – NDA 19-922

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data- NDA 19-922

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. Storage/Dispensing Conditions:

NDA: Store at 2° to 30°C.

ANDA: Store at 2° to 30°C.

(b) (4)

4. Product Line:

The innovator markets their product in two ampule sizes. 1 mL and 2 mL ampules utilizing the concentration of 10mg/mL.

The applicant proposes to market their product in 1 mL and 2 mL vials utilizing the 10 mg/mL concentration as well.

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the **statement of components appearing on page 66, Vol. A. 1.1.**

6. Container/Closure(See page 0595 in Vol. A.. 1.2)

Containers: Type 1 glass container

Closure:BVL stopper with flip-off seal

7. All manufacturing will be done by Ben Venue Laboratories for Bedford Laboratories, Inc. (See pg. 00112 in vol. A. 1.1)

Date of Review: 2/21/03

Date of Submission: 12/18/02

Primary Reviewer: Jim Barlow

Date: 2/21/03

Team Leader: John Grace

Date: 2/26/2003

cc:

ANDA: 76-582

DUP/DIVISION FILE

HFD-613/JBarlow/JGrace (no cc)

V:\FIRMSAM\BEDFORD\LTRS&REV\76582na1.i.doc

Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 76582

CHEMISTRY REVIEWS

ANDA 76-582

**Fenoldopam Mesylate Injection, USP
10 mg/mL, 1 mL and 2 mL vials**

Bedford Laboratories

**Bing Cai, Ph.D
Chemistry Division I, OGD**

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Chemistry Review Data Sheet

1. ANDA 76-582

2. REVIEW #: 4

REVIEW DATE: August 10, 2004
August 26, 2004

4. REVIEWER: Bing Cai, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
<i>Bedford</i>	
Original Submission	Dec-18-2002
Amendment (b) (4)	Aug-18-2003
Amendment	Aug-18-2003
Amendment	Aug-25-2003
Amendment (microbiology)	Nov-14-2003
Amendment (Labeling)	Feb-03-2004
Amendment (Labeling)	Aug-12-2004
 <i>FDA</i>	
Acceptable for Filing (Dec-19-2002)	Jan-23-2003
Labeling review (1 st cycle)	Feb-26-2003
CMC, NA letter	May-29-2003
Bio, Satisfactory	Jun-19-2003
CMC NA Letter	Nov-10-2003
Micro Deficient	Jan-15-2004
CMC/Minor Satisfactory	Apr-15-2004
Approvable Letter	Apr-20-2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (minor)	Jul-09-2004
Amendment (minor)	Jul-27-2004

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Bedford Laboratories
Address: 300 Northfield Road
Bedford, OH 44146
Representative: Molly L. Rapp
Telephone: 440-201-3576

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Fenoldopam Mesylate

9. LEGAL BASIS FOR SUBMISSION: 505 (j)

Paragraph I Certification is provided on page 5.

Innovator Product:: Corlopan® 10 mg/mL; 1 mL and 2 mL per vial.
(NDA #: 19-922, Approval Date: 09/23/97)
Innovator Company: Abbott

	Patent #/Expiration Date	Use Code
Patent	None	None
Exclusivity	Expired: 09/23/2002	NCE
	Expires: April 1, 2007	1-42

10. PHARMACOL. CATEGORY: Rapid-acting Vasodilator

11. DOSAGE FORM: Liquid Injectable

12. STRENGTH/POTENCY: 10 mg/mL, 1 ml/vial, 10 mg/mL, 2 ml/vial

13. ROUTE OF ADMINISTRATION: Intravenous Infusion

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

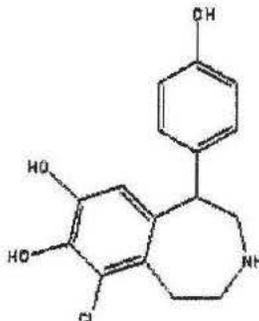
SPOTS product – Form Completed

Not a SPOTS product

CHEMISTRY REVIEW

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_{16}H_{16}ClNO_3 \cdot CH_4SO_3$ 401.87 [67227-57-0].

1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate (salt). 6-Chloro-2,3,4,5-tetrahydro-1-(p-hydroxyphenyl)-1 H-3-benzazepine-7,8-diol methanesulfonate (salt).

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	adequate	04/14/04	B. Cai, Ph.D.
	III			4			
	III			4			
	V			7	Adequate	7/8/04	B. Pillari

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMEN-DATION	DATE	REVIEWER
Microbiology	Acceptable	2/17/04	M. Stevens-Riley
EES	Acceptable	08/04/03	J. D'Ambrogio
Methods Validation	N/A (USP)		
Labeling	Acceptable	8/26/04	J. Barlow
Bioequivalence	Acceptable	6/19/03	J. Osterhout
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-582

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

No CMC changes since last TA or 4/20/04.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Bedford's proposed drug product, Fenoldopam Mesylate Injection USP, 10 mg/mL, 1 mL and 2 mL vials, is based on the reference listed drug (RLD), Corlopan[®] 10 mg/mL; 1 mL and 2 mL per vial, product of Abbott (NDA # 19-022, Approval Date: 09/23/97). The drug product is listed in the current USP.

Bedford's drug product is indicated for in-patient treatment for short-term (up to 48 hours) management of severe hypertension when rapid, but quickly reversible, emergency reduction of blood pressure is clinically indicated. Bedford's drug product not only contains the same active ingredients as the innovator's product but its formulation is Q1/Q2 to the innovator's product. The route of administration (intravenous), dosage forms (sterile Injection), and strength are also the same.

The sterility assurance information for manufacturing the exhibit batches as well as the commercial batches are found acceptable per 2/17/04.

The drug substance, Fenoldopam Mesylate USP, is a white to off white powder. It is sparingly soluble in water, ethanol and is freely soluble in propylene glycol. Fenoldopam is a racemic mixture with the R-isomer responsible for the biological activity. It is listed in the current USP. The drug substance used by Bedford is manufactured by (b) (4). The manufacturing information is submitted in a separate Type II DMF # (b) (4). The DMF has been found *adequate* as of April 14, 2004 by this reviewer.

CHEMISTRY REVIEW

Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

Bedford's drug product, Fenoldopam Mesylate Injection USP, 10mg/mL is a
(b) (4)
(b) (4). It is supplied in single-dose vials (1 mL and 2 mL). It must be
diluted by an IV solution (40 mcg/mL) before giving it to a patient.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable.

III. Administrative

A. Reviewer's Signature

Bing Cai, Ph.D.

B. Endorsement Block

HFD-620/BCai, Ph.D./Review Chemist/08/10/04
HFD-620/SLiu, Ph.D./Chemistry Team Leader/8/12/04
HFD-617/WPamphile, Pharm.D./Project Manager/10/7/04

SH. Liu 10/8/04

C. CC Block

CHEMISTRY REVIEW

Chemistry Assessment Section

Chemistry Assessment

20. COMPONENTS AND COMPOSITION: Satisfactory per CR#1

The composition and function of ingredients of the drug product/bulk solution is provided (Original ANDA, pp. 66-67,) and is presented in the following table:

Ingredient	Grade	Pharm. Function	Per ml. (mg)	Commercial Batch/2 ml.	Commercial Batch/1 ml.	ANDA Batch
Fenoldopam Mesylate	USP	Active	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Propylene Glycol	USP	(b) (4)	518	(b) (4)	(b) (4)	(b) (4)
Citric Acid	USP	(b) (4)	3.44	(b) (4)	(b) (4)	(b) (4)
Sodium Citrate Dihydrate	USP	(b) (4)	0.61	(b) (4)	(b) (4)	(b) (4)
Sodium Metabisulfite	NF	(b) (4)	1.0	(b) (4)	(b) (4)	(b) (4)

21. FACILITIES: Satisfactory per CR#1

22. SYNTHESIS: Satisfactory per CR#3

The DMF (b) (4) has been reviewed at this cycle and it is found adequate.



Drug Master File No. (b) (4) has been found adequate in CR#3.

CHEMISTRY REVIEW

Chemistry Assessment Section

(b) (4)

30. **MICROBIOLOGY:** Adequate per 2/17/04

31. **SAMPLES AND RESULTS/METHODS VALIDATION STATUS**

Not Required (USP DS/DP).

32. **LABELING** Acceptable by J. Barlow or 8/26/04

Items that reviewed by Chemist: Sat. per CR#1

33. **ESTABLISHMENT INSPECTION:** Acceptable on 8/4/03

Firm	Function	EES
Ben Venue Labs INC Bedford, OH	DP Manufacturer	Acceptable

(b) (4)

34. **BIOEQUIVALENCE:** Acceptable per 6/19/03 by J. L. Osterhout

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:**

Satisfactory per CR#1.

CHEMISTRY REVIEW

Chemistry Assessment Section

cc: ANDA 76-582
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates)

HFD-620/Bing Cai, Ph.D./08/10/04

B. Cai 10/8/04

HFD-620/Shing Liu, Ph.D./8/12/04

S.H. Liu 10/8/04

HFD-617/Wanda Pamphile, Pharm.D. C.Kiester for/10/7/04

Wanda Pamphile 10/8/04

F/T by:ard/10/8/04

V:\FIRMS\AMBEDFORD\LTRS&REV\76582cr4.DOC

TYPE OF LETTER: APPROVABLE

ANDA 76-582

**Fenoldopam Mesylate Injection, USP
10 mg/mL, 1 mL and 2 mL vials**

Bedford Laboratories

**Bing Cai, Ph.D
Chemistry Division I, OGD**

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Chemistry Review Data Sheet

1. ANDA 76-582
2. REVIEW #: 3
3. REVIEW DATE: February 24, 2004
April 14, 2004 (Revised)
4. REVIEWER: Bing Cai, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
<i>Bedford</i>	
Original Submission	Dec-18-2002
NC	Mar-18-2003
Amendment [REDACTED] (b) (4)	Aug-18-2003
Amendment	Aug-18-2003
Amendment	Aug-25-2003
Amendment(Labeling)	Mar-19-2004
<i>FDA</i>	
Acceptable for Filing (Dec-19-2002)	Jan-23-2003
Labeling review (1 st cycle)	Feb-26-2003
CMC, NA letter	May-29-2003
NA Letter	Nov-10-2003
Micro Deficient	Jan-15-2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (microbiology)	Nov-14-2003
Amendment (minor)	Feb-03-2004



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Bedford Laboratories
 Address: 300 Northfield Road
 Bedford, OH 44146
 Representative: Molly L. Rapp
 Telephone: 440-201-3576

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Fenoldopam Mesylate

9. LEGAL BASIS FOR SUBMISSION: 505 (j)

Paragraph I Certification is provided on page 5.

Innovator Product:: Corloпам® 10 mg/mL; 1 mL and 2 mL per vial
 (NDA #: 19-922, Approval Date: 09/23/97)
 Innovator Company: Abbott

	Patent #/Expiration Date	Use Code
Patent	None	None
Exclusivity	Expired: 09/23/2002	NCE

10. PHARMACOL. CATEGORY: Rapid-acting Vasodilator

11. DOSAGE FORM: Liquid Injectable

12. STRENGTH/POTENCY: 10 mg/mL, 1 ml/vial, 10 mg/mL, 2 ml/vial

13. ROUTE OF ADMINISTRATION: Intravenous Infusion

14. Rx/OTC DISPENSED: X Rx OTC

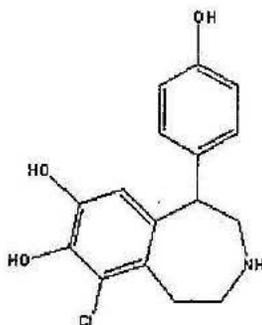
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Chemistry Review Data Sheet

X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_{16}H_{16}ClNO_3 \cdot CH_4SO_3$ 401.87 [67227-57-0].

1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate (salt). 6-Chloro-2,3,4,5-tetrahydro-1-(p-hydroxyphenyl)-1 H-3-benzazepine-7,8-diol methanesulfonate (salt).

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	adequate	04/14/04	B. Cai, Ph.D.
	III			4			
	III			4			
	V			7	inadequate	10/08/03	M. Stevens-Riley

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Chemistry Review Data Sheet

Other codes indicate why the DMF was not reviewed, as follows:

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMEN-DATION	DATE	REVIEWER
Microbiology	Acceptable	2/17/04	M. Stevens-Riley
EES	Acceptable	08/04/03	J. D'Ambrogio
Methods Validation	N/A (USP)		
Labeling	Pending		J.Barlow
Bioequivalence	Acceptable	6/19/03	J. Osterhout
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-582

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry manufacturing and control are approvable.
Microbiology issues are resolved and approvable.

Pending labeling review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Bedford's proposed drug product, Fenoldopam Mesylate Injection USP, 10 mg/mL, 1 mL and 2 mL vials, is based on the reference listed drug (RLD), Corlopan[®] 10 mg/mL; 1 mL and 2 mL per vial, product of Abbott (NDA # 19-022, Approval Date: 09/23/97). The drug product is listed in the current USP.

Bedford's drug product is indicated for in-patient treatment for short-term (up to 48 hours) management of severe hypertension when rapid, but quickly reversible, emergency reduction of blood pressure is clinically indicated. Bedford's drug product not only contains the same active ingredients as the innovator's product but its formulation is Q1/Q2 to the innovator's product. The route of administration (intravenous), dosage forms (sterile Injection), and strength are also the same.

The sterility assurance information for manufacturing the exhibit batches as well as the commercial batches are found acceptable per 2/17/04.

The drug substance, Fenoldopam Mesylate USP, is a white to off white powder. It is sparingly soluble in water, ethanol and is freely soluble in propylene glycol. Fenoldopam is a racemic mixture with the R-isomer responsible for the biological activity. It is listed in the current USP. The drug substance used by Bedford is manufactured by [REDACTED] (b) (4). The

Executive Summary Section

manufacturing information is submitted in a separate Type II DMF # (b) (4) The DMF has been found *adequate* as of April 14, 2004 by this reviewer.

B. Description of How the Drug Product is Intended to be Used

Bedford's drug product, Fenoldopam Mesylate Injection USP, 10mg/mL is a

(b) (4)
(b) (4) It is supplied in single-dose vials (1 mL and 2 mL). It must be diluted by an IV solution (40 mcg/mL) before giving it to a patient.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable pending labeling issue.

III. Administrative**A. Reviewer's Signature**

Bing Cai, Ph.D.

B. Endorsement Block

HFD-620/BCai, Ph.D./Review Chemist/02/024/04, 02/27/04

HFD-620/SLiu, Ph.D./Chemistry Team Leader/3/2/04

HFD-617/WPamphile, Pharm.D./Project Manager/

S.H. Liu 4/15/04

C. CC Block

Chemistry Assessment Section

Chemistry Assessment**20. COMPONENTS AND COMPOSITION: Satisfactory per CR#1**

The composition and function of ingredients of the drug product/bulk solution is provided (Original ANDA, pp. 66-67,) and is presented in the following table:

Ingredient	Grade	Pharm. Function	Per mL (mg)	Commercial Batch/2 mL	Commercial Batch/1 mL	ANDA Batch (b) (4)
Fenoldopam Mesylate	USP	Active	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Propylene Glycol	USP	(b) (4)	518	(b) (4)	(b) (4)	(b) (4)
Citric Acid	USP	(b) (4)	3.44	(b) (4)	(b) (4)	(b) (4)
Sodium Citrate Dihydrate	USP	(b) (4)	0.61	(b) (4)	(b) (4)	(b) (4)
Sodium Metabisulfite	NF	(b) (4)	1.0	(b) (4)	(b) (4)	(b) (4)

21. FACILITIES: Satisfactory per CR#1**22. SYNTHESIS: Become Satisfactory**

The DMF (b) (4) has been reviewed at this cycle and it is found adequate.



Chemistry Assessment Section

(b) (4)

30. **MICROBIOLOGY:** Adequate per 2/17/04

31. **SAMPLES AND RESULTS/METHODS VALIDATION STATUS**
Not Required (USP DS/DP).

32. **LABELING** Pending ISSUE

Items that reviewed by Chemist: Sat. per CR#1

33. **ESTABLISHMENT INSPECTION:** Acceptable on 8/4/03

Firm	Function	EES
Ben Venue Labs INC Bedford, OH	DP Manufacturer	Acceptable

(b) (4)

34. **BIOEQUIVALENCE:** Acceptable per 6/19/03 by J. L Osterhout

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:**

Satisfactory per CR#1.



Chemistry Assessment Section

cc: ANDA 76-582
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/Bing Cai, Ph.D./02/27/04

Handwritten: N.H. 4/15/04

HFD-620/Shing Liu, Ph.D./3/2/04

Handwritten: S.H. Liu 4/15/04

HFD-617/Wanda Pamphile, Pharm.D./4/15/04

Handwritten: ~~WF~~ 4/15/04

F/T by:ard/4/15/04

V:\FIRMSAMBEDFORD\LTRS&REV\76582cr3.DOC

TYPE OF LETTER: APPROVABLE – (Labeling issue pending)

ANDA 76-582

**Fenoldopam Mesylate Injection, USP
10 mg/mL, 1 mL and 2 mL vials**

Bedford Laboratories

**Bing Cai, Ph.D
Chemistry Division I, OGD**

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A. Reviewer's Signature	8
B. Endorsement Block	8
C. CC Block.....	8
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Chemistry Review Data Sheet

1. ANDA 76-582 (1st Generic Drug)
2. REVIEW #: 2
3. REVIEW DATE: September 31, 2003
4. REVIEWER: Bing Cai, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
<i>Bedford</i>	
Original Submission	Dec-18-2002
NC	Mar-18-2003
Amendment [REDACTED] (b) (4)	Aug-18-2003
<i>FDA</i>	
Acceptable for Filing (Dec-19-2002)	Jan-23-2003
Labeling review (1 st cycle)	Feb-26-2003
CMC, NA letter	May-29-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	Aug-18-2003
Amendment	Aug-25-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Bedford Laboratories
 Address: 300 Northfield Road
 Bedford, OH 44146
 Representative: Molly Rapp
 Telephone: 440-201-3576



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Fenoldopam Mesylate

9. LEGAL BASIS FOR SUBMISSION: 505 (j)

Paragraph I Certification is provided on page 5.

Innovator Product:: Corloпам® 10 mg/mL; 1 mL and 2 mL per vial
 (NDA #: 19-922, Approval Date: 09/23/97)

Innovator Company: Abbott

	Patent #/Expiration Date	Use Code
Patent	None	None
Exclusivity	Expired: 09/23/2002	NCE

10. PHARMACOL. CATEGORY: Rapid-acting Vasodilator

11. DOSAGE FORM: Liquid Injectable

12. STRENGTH/POTENCY: 10 mg/mL, 1 ml/vial, 10 mg/mL, 2 ml/vial

13. ROUTE OF ADMINISTRATION: Intravenous Infusion

14. Rx/OTC DISPENSED: Rx OTC

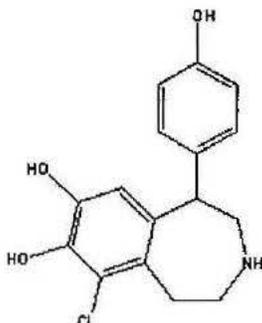
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_{16}H_{16}ClNO_3 \cdot CH_4SO_3$ 401.87 [67227-57-0].

1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate (salt). 6-Chloro-2,3,4,5-tetrahydro-1-(p-hydroxyphenyl)-1 H-3-benzazepine-7,8-diol methanesulfonate (salt).

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW	COMMENTS
(b) (4)	II		(b) (4)	1	inadequate	09/30/03	B. Cai, Ph.D.
	III			4			
	III			4			
	V			7	inadequate	10/08/03	M. Stevens-Riley

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMEN-DATION	DATE	REVIEWER
Microbiology	Deficient	10/10/03	M. Stevens-Riley
EES	Acceptable	08/04/03	J. D' Ambrogio
Methods Validation	N/A (USP)		
Labeling	Pending		
Bioequivalence	Acceptable	6/19/03	J. Osterhout
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-582

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry manufacturing and controls are not approvable. The labeling review is pending, and Micro is deficient. It is recommended that a Not Approvable, Minor deficiencies, letter be sent to the applicant.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Bedford's proposed drug product, Fenoldopam Mesylate Injection USP, 10 mg/mL, 1 mL and 2 mL vials, is based on the reference listed drug (RLD), Corlopan[®] 10 mg/mL; 1 mL and 2 mL per vial, product of Abbott (NDA # 19-022, Approval Date: 09/23/97). The drug product is listed in the current USP.

Bedford's drug product is indicated for in-patient treatment for short-term (up to 48 hours) management of severe hypertension when rapid, but quickly reversible, emergency reduction of blood pressure is clinically indicated. Bedford's drug product not only contains the same active ingredients as the innovator's product but its formulation is Q1/Q2 to the innovator's product. The route of administration (intravenous), dosage forms (sterile Injection), and strength are also the same.

The sterility assurance information for manufacturing the exhibit batches as well as the commercial batches is deficient.

The drug substance, Fenoldopam Mesylate USP, is a white to off white powder. It is sparingly soluble in water, ethanol and is freely soluble in propylene glycol. Fenoldopam is a racemic mixture with the R-isomer responsible for the biological activity. It is listed in the current USP. The drug substance used by Bedford is manufactured by (b) (4). The manufacturing information is submitted in a separate Type II DMF # (b) (4). The DMF has been found *inadequate* as of September 30, 2003 by this reviewer.

Executive Summary Section**B. Description of How the Drug Product is Intended to be Used**

Bedford's drug product, Fenoldopam Mesylate Injection USP, 10mg/mL is a

(b) (4). It is supplied in single-dose vials (1 mL and 2 mL). It must be diluted by an IV solution (40 mcg/mL) before give it to a patient.

C. Basis for Approvability or Not-Approval Recommendation

This application is not approvable due to the CMC deficiencies found in the following areas:

- the drug substance controls and other related issues.

Labeling review pending
Micro deficient.

III. Administrative**A. Reviewer's Signature**

Bing Cai, Ph.D.

B. Endorsement Block

HFD-620/BCai, Ph.D./Review Chemist/10/1/31
HFD-620/SLiu, Ph.D./Chemistry Team Leader/
HFD-617/WPamphile, Pharm.D./Project Manager/

for Rstandard 11/18/03

C. CC Block

Chemistry Assessment Section

Chemistry Assessment**20. COMPONENTS AND COMPOSITION: Satisfactory per CR#1**

The composition and function of ingredients of the drug product/bulk solution is provided (Original ANDA, pp. 66-67,) and is presented in the following table:

Ingredient	Grade	Pharm. Function	Per mL (mg)	Commercial Batch/2 mL	Commercial Batch/1 mL	ANDA Batch
Fenoldopam Mesylate	USP	Active				(b) (4)
Propylene Glycol	USP	(b) (4)	518			(b) (4)
Citric Acid	USP		3.44			
Sodium Citrate Dihydrate	USP		0.61			
Sodium Metabisulfite	NF		1.0			(b) (4)

(b) (4)

21. FACILITIES: Satisfactory per CR#1**22. SYNTHESIS: Unsatisfactory**

(b) (4)

Chemistry Assessment Section

(b) (4)

30. MICROBIOLOGY: Deficient

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
Not Required (USP DS/DP).

32. LABELING Pending review

Items that reviewed by Chemist: Sat. per CR#1

33. ESTABLISHMENT INSPECTION: Pending

Firm	Function	EES
Ben Venue Labs INC Bedford, OH	DP Manufacturer	Acceptable

(b) (4)



Chemistry Assessment Section

34. BIOEQUIVALENCE: Acceptable per 6/19/03 by J. L Osterhout

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Satisfactory per CR#1.



Chemistry Assessment Section

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-582

APPLICANT:

Bedford Laboratories

DRUG PRODUCT: **Fenoldopam Mesylate Injection USP, 10 mg/mL, 1 mL and 2 mL vials**

The deficiency presented below represents a MINOR deficiency.

A. Deficiency:

Drug Master File No. (b) (4) has been found deficient. We have notified the DMF holder, (b) (4) of the deficiencies. Please do not respond to this letter until the DMF holder has informed you that a complete response to the DMF deficiencies has been submitted to the agency.

B. In addition to responding to the deficiency presented above, please note and acknowledge the following comments in your response:

1. Microbiology deficiencies were communicated to you via facsimile on October 10, 2003. You should address the issues in the October 10 communication prior to or concurrent with your response to this communication.
2. Your labeling information is pending review. Deficiencies, if any, will be communicated separately.
3. Please provide all available long-term drug product stability data (samples stored at conditions of room temperature and 2-8°C).

Sincerely yours,


Rashmikant M. Patel, Ph.D.

Director

Division of Chemistry I

Office of Generic Drugs

Center for Drug Evaluation and Research



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 76-582
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/Bing Cai, Ph.D./10/01/03

10/10/03

HFD-620/Shing Liu, Ph.D./ S.H. Liu 11/13/03

HFD-617/Wanda Pamphile, Pharm.D./ ~~11/13/03~~ 11/13/03

F/T by:

\\CDS013\OGDS11\FIRMS\AMBEDFORD\LTRS&REV\76582cr2.DOC

TYPE OF LETTER: NOT APPROVABLE - MINOR

ANDA 76-582

**Fenoldopam Mesylate Injection, USP
10 mg/mL, 1 mL and 2 mL vials**

Bedford Laboratories

**Bing Cai, Ph.D
Chemistry Division I, OGD**

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Chemistry Review Data Sheet

1. ANDA 76-582 (1st Generic Drug)
2. REVIEW #: 1
3. REVIEW DATE: April 2-15 2003
4. REVIEWER: Bing Cai, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date*Bedford*

Original Submission

Dec-18-2002

NC

Mar-18-2003

FDA

Acceptable for Filing (Dec-19-2002)

Jan-23-2003

Labeling review (1st cycle)

Feb-26-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Bedford Laboratories

Address: 300 Northfield Road
Bedford, OH 44146

Representative: Molly Rapp

Telephone: 440-201-3576



8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Fenoldopam Mesylate

9. LEGAL BASIS FOR SUBMISSION: 505 (j)

Paragraph I Certification is provided on page 5.

Innovator Product:: Corlopan® 10 mg/mL; 1 mL and 2 mL per vial
(NDA #: 19-922, Approval Date: 09/23/97)

Innovator Company: Abbott

	Patent #/Expiration Date	Use Code
Patent	None	None
Exclusivity	Expired: 09/23/2002	NCE

10. PHARMACOL. CATEGORY: Rapid-acting Vasodilator

11. DOSAGE FORM: Liquid Injectable

12. STRENGTH/POTENCY: 10 mg/mL, 1 ml/vial, 10 mg/mL, 2 ml/vial

13. ROUTE OF ADMINISTRATION: Intravenous Infusion

14. Rx/OTC DISPENSED: Rx OTC

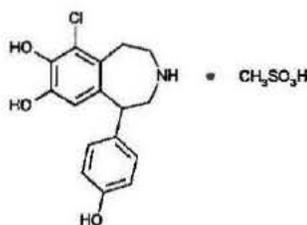
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product -- Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_{16}H_{16}ClNO_3 \cdot CH_4SO_3$ 401.87 [67227-57-0].

1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate (salt). 6-Chloro-2,3,4,5-tetrahydro-1-(p-hydroxyphenyl)-1 H-3-benzazepine-7,8-diol methanesulfonate (salt).

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	inadequate	04/08/03	
	III			4			
	III			4			
	V			7			To be reviewed by microbiologist

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMEN-DATION	DATE	REVIEWER
Microbiology	Pending		
EES	Pending		
Methods Validation	N/A (USP)		
Labeling	Deficient	2/26/03	J. Barlow
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-582

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry manufacturing and controls are not approvable. Labeling review is deficient. Micro and bioequivalence review are pending. It is recommended that a Not Approvable, Minor deficiencies, letter be sent to the applicant.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Bedford's proposed drug product, Fenoldopam Mesylate Injection USP, 10 mg/mL, 1 mL and 2 mL vials, is based on the reference listed drug (RLD), Corlopan[®] 10 mg/mL; 1 mL and 2 mL per vial, product of Abbott (NDA # 19-022, Approval Date: 09/23/97). The drug product is listed in the current USP.

Bedford's drug product is indicated for the treatment for the in-hospital, short-term (up to 48 hours) management of severe hypertension when rapid, but quickly reversible, emergency reduction of blood pressure is clinically indicated. Bedford's drug product not only contains the same active ingredients as the innovator's product but its formulation is Q1/Q2 to the innovator's product. The route of administration (intravenous), dosage forms (sterile Injection), and strength are also the same.

The sterility assurance information for manufacturing the exhibit batches as well as the commercial batches is pending for review.

The drug substance, Fenoldopam Mesylate USP, is a white to off white powder. It is sparingly soluble in water, ethanol and is freely soluble in propylene glycol. Fenoldopam is a racemic mixture with the R-isomer responsible for the biological activity. It is listed in the current USP. The drug substance used by Bedford is manufactured by (b) (4). The manufacturing information is submitted in a separate Type II DMF # (b) (4). The DMF has been found *inadequate* as of April 8, 2003 by this reviewer. It is also

CHEMISTRY REVIEW

Executive Summary Section

noted the DS manufacture's capacity may be below the requirement of the applicant's demand based on the information provided in the current DMF.

B. Description of How the Drug Product is Intended to be Used

Bedford's drug product, Fenoldopam Mesylate Injection USP, 10mg/mL is a

(b) (4) It is supplied in single-dose vials (1 mL and 2 mL). It must be diluted by an IV solution (40 mcg/mL) before give it to a patient.

C. Basis for Approvability or Not-Approval Recommendation

This application is not approvable due to the CMC deficiencies found in the following areas:

(b) (4)

Micro review, bioequivalence review and EER are pending.
Labeling is deficient.

III. Administrative

A. Reviewer's Signature

Bing Cai, Ph.D.

B. Endorsement Block

HFD-620/BCai, Ph.D./Review Chemist/04/15/03.05/07/03

HFD-620/SLiu, Ph.D./Chemistry Team Leader/

HFD-617/WPamphile, Pharm.D./Project Manager/

C. CC Block

Chemistry Assessment Section

Chemistry Assessment

Note: items 1 – 19 are now covered in the Review Data Sheet.

20. COMPONENTS AND COMPOSITION: Satisfactory

The composition and function of ingredients of the drug product/bulk solution is provided (pp. 66-67) and is presented in the following table:

Ingredient	Grade	Pharm. Function	Per mL (mg)	Commercial Batch/2 mL	Commercial Batch/1 mL	ANDA Batch
Fenoldopam Mesylate	USP	Active	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Propylene Glycol	USP	(b) (4)	518	(b) (4)	(b) (4)	(b) (4)
Citric Acid	USP	(b) (4)	3.44	(b) (4)	(b) (4)	(b) (4)
Sodium Citrate Dihydrate	USP	(b) (4)	0.61	(b) (4)	(b) (4)	(b) (4)
Sodium Metabisulfite	NF	(b) (4)	1.0	(b) (4)	(b) (4)	(b) (4)

Comments: The components/compositions used in applicant's formulation are the same as those used in the Reference Listed Drug Product. Comparison between generic drug and Reference Drug product is provided on page 7. The inactive ingredients in the formulation are found to be present below levels cited in the FDA Inactive Ingredient Guide for approved drug products. All ingredients listed in the "Components and Composition" Section of this ANDA are consistent with those listed in the applicant's label insert. The pH of the solution is 2.8-3.8. It is satisfactory.

21. FACILITIES: Satisfactory

The drug product will be manufactured and tested (release/stability) at the following facility:

Ben Venue Laboratories, Inc.
270 Northfield Road
Bedford, OH 44146
Drug Establishment # 1519257

Copy of cGMP certification is provided (page 113). It is satisfactory. EER for Ben Venue has been issued and the result is pending.

Chemistry Assessment Section



(b) (4)

30. MICROBIOLOGY: Pending

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
Not Required (USP DS/DP).

32. LABELING Unsatisfactory.

Labeling review (1st cycle) completed (02/26/03). Deficiencies found.

Items reviewed by Chemist:

Description Section

- a. Structures: Satisfactory
- b. Chemical names: Satisfactory
- c. Empirical formulas: Satisfactory
- d. Name of the inactives: Satisfactory
- e. Physical and Chemical properties of DS: Satisfactory

2. How Supplied Section

- a. Packaging: 10 mg/mL 1 mL and 2 mL Vials
- b. Storage Conditions: Store at 2-30 °C

33. ESTABLISHMENT INSPECTION: Pending

Firm	Function	EES
Ben Venue Labs INC Bedford, OH	DP Manufacturer	Pending

(b) (4)

34. BIOEQUIVALENCE Pending as of 04/15/03.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

The applicant has requested categorical exclusion from the requirement of an Environmental Assessment Report (p. 843). It is satisfactory.

Chemistry Assessment Section

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANTANDA: 76-582APPLICANT: Bedford LaboratoriesDRUG PRODUCT: **Fenoldopam Mesylate Injection USP 10 mg/mL, 1 mL and
2 mL vials**

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File No. (b) (4) has been found deficient. We have notified the DMF holder, (b) (4) of the deficiencies. Please do not respond to this deficiency letter until the DMF holder submits a complete response to the Agency.

2.

(b) (4)

3.

4.

5.

6.

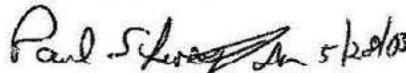
7.



Chemistry Assessment Section

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:
1. Please provide all available long-term drug product stability data (samples stored at conditions of room temperature and 2-8°C).
 2. Your labeling information is found deficient. Labeling deficiencies also need to be addressed in your reply.
 3. Your bioequivalence information and sterility assurance are pending review. Deficiencies, if any, will be communicated separately.
 4. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.
 5.  (b) (4)

Sincerely yours,



Rashmikant M. Patel, Ph.D.

Director

Division of Chemistry I

Office of Generic Drugs

Center for Drug Evaluation and Research

cc: ANDA 76-582
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/Bing Cai, Ph.D./05/07/03

CHEMISTRY REVIEW

Chemistry Assessment Section

cc: ANDA 76-582
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/Bing Cai, Ph.D./05/07/03

Ph 5/24/03

HFD-620/Shing Liu, Ph.D./05/07/03

S.H. Liu 5/22/03

HFD-617/Wanda Pamphile, Pharm.D./

WF 5/22/03

F/T by: gp/05/22/03

V:\FIRMS\AMBEDFORD\LTRS&REV\76582cr1r.DOC

TYPE OF LETTER: NOT APPROVABLE - MINOR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 76582

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

Review for HFD-620

13 February 2004

ANDA: 76-582

Drug Product Name

Proprietary: Corlopam

Non-proprietary: Fenoldopam Mesylate Injection USP

Drug Product Classification: N/A

Review Number: 3

Subject of this Review

Submission Date: February 3, 2004

Receipt Date: February 4, 2004

Consult Date: N/A

Date Assigned for Review: February 6, 2004

Submission History (for amendments only)

Date(s) of Previous Submission(s): December 18, 2002, August 18, 2003, November 14, 2003

Date(s) of Previous Micro Review(s): August 27, 2003, December 12, 2003

Applicant/Sponsor

Name: Bedford Laboratories

**Address: 300 Northfield Road
Bedford, Ohio 44146**

Representative: Molly Rapp

Telephone: 440-201-3576

Name of Reviewer: Marla Stevens-Riley

Conclusion: Recommended for approval on the basis on sterility assurance

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUPPLEMENT:** N/A
 2. **SUPPLEMENT PROVIDES FOR:** N/A
 3. **MANUFACTURING SITE:** Ben Venue Laboratories
270 Northfield Rd.
Bedford, Ohio 44146
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** sterile solution, intravenous administration, 10 mg/mL as 1 mL and 2 mL per 2 mL (b) (4)
 5. **METHOD(S) OF STERILIZATION:** (b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** vasodilator
- B. **SUPPORTING/RELATED DOCUMENTS:** DMF (b) (4)
(b) (4)
- C. **REMARKS:** The subject amendment is a response to the Microbiology deficiency letter dated January 16, 2004.

filename: v:microrev\76-582a2.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability – Recommended for approval on the basis of sterility assurance**
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –N/A**

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** (b) (4)
(b) (4)
- B. Brief Description of Microbiology Deficiencies –none**
- C. Assessment of Risk Due to Microbiology Deficiencies - The risk to public health associated with this product is minimal. All deficiencies have been resolved.**

III. Administrative

A. Reviewer's Signature

Maria Stevens-Riley 2/17/04

- B. Endorsement Block**
 M. Stevens-Riley, Ph.D.
 N. J. Sweeney, Ph.D.

N. J. Sweeney 2-17-04

- C. CC Block**
 cc:
 Original ANDA 76-582
 Division File
 Field Copy

Product Quality Microbiology Review

Review for HFD-620

12 December 2003

ANDA: 76-582

Drug Product Name

Proprietary: Corloпам

Non-proprietary: Fenoldopam Mesylate Injection USP

Drug Product Classification: N/A

Review Number: 2

Subject of this Review

Submission Date: November 14, 2003

Receipt Date: November 17, 2003

Consult Date: N/A

Date Assigned for Review: November 25, 2003

Submission History (for amendments only)

Date(s) of Previous Submission(s): December 18, 2002 and August 18, 2003

Date(s) of Previous Micro Review(s): August 27, 2003

Applicant/Sponsor

Name: Bedford Laboratories

**Address: 300 Northfield Road
Bedford, Ohio 44146**

Representative: Molly Rapp

Telephone: 440-201-3576

Name of Reviewer: Marla Stevens-Riley

Conclusion: Not recommended for approval on the basis on sterility assurance

Product Quality Microbiology Data Sheet

- A.**
1. **TYPE OF SUPPLEMENT:** N/A
 2. **SUPPLEMENT PROVIDES FOR:** N/A
 3. **MANUFACTURING SITE:** Ben Venue Laboratories
270 Northfield Rd.
Bedford, Ohio 44146
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** sterile solution, intravenous administration, 10 mg/mL as 1 mL and 2 mL per 2 mL (b) (4)
 5. **METHOD(S) OF STERILIZATION:** (b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** vasodilator
- B.** **SUPPORTING/RELATED DOCUMENTS:** (b) (4)
(b) (4)
- C.** **REMARKS:** The subject amendment is a response to the Microbiology deficiency letter dated October 10, 2003.

filename: v:microrev\76-582a1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability – Not recommended for approval on the basis of sterility assurance**
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –N/A**

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** (b) (4)
(b) (4)
- B. Brief Description of Microbiology Deficiencies –**The DMF is deficient, and the ANDA submission has incomplete information regarding filter validation information.
- C. Assessment of Risk Due to Microbiology Deficiencies -**The risk to public health associated with these deficiencies is moderate.

III. Administrative

- A. Reviewer's Signature** Marka Stevens-Riley
- B. Endorsement Block**
 M. Stevens-Riley, Ph.D. 12/23/03
 N. J. Sweeney, Ph.D. N. J. Sweeney 1-15-04
- C. CC Block**
 cc:
 Original ANDA 76-582
 Division File
 Field Copy

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

ANDA: 76-582

APPLICANT: Bedford Laboratories

DRUG PRODUCT: Fenoldopam Mesylate Injection USP 10 mg/mL

Microbiology Deficiencies:

1.

2.

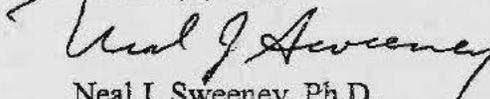
3.

4.

(b) (4)

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,



Neal J. Sweeney, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

Product Quality Microbiology Review

Review for HFD-620

27 August 2003

ANDA: 76-582

Drug Product Name

Proprietary: Corlopam

Non-proprietary: Fenoldopam Mesylate Injection USP

Drug Product Classification: N/A

Review Number: 1

Subject of this Review

Submission Date: December 18, 2002 and August 18, 2003 (telephone amendment)

Receipt Date: December 19, 2002 and August 19, 2003

Consult Date: N/A

Date Assigned for Review: August 8, 2003

Submission History (for amendments only)

Date(s) of Previous Submission(s):

Date(s) of Previous Micro Review(s):

Applicant/Sponsor

Name: Bedford Laboratories

**Address: 300 Northfield Road
Bedford, Ohio 44146**

Representative: Molly Rapp

Telephone: 440-201-3576

Name of Reviewer: Marla Stevens-Riley

Conclusion: Not recommended for approval on the basis on sterility assurance

Product Quality Microbiology Data Sheet

- A.
1. TYPE OF SUPPLEMENT: N/A
 2. SUPPLEMENT PROVIDES FOR: N/A
 3. MANUFACTURING SITE: Ben Venue Laboratories
270 Northfield Rd.
Bedford, Ohio 44146
 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: sterile solution, intravenous administration, 10 mg/mL as 1 mL and 2 mL per 2 mL (b) (4)
 5. METHOD(S) OF STERILIZATION: (b) (4)
 6. PHARMACOLOGICAL CATEGORY: vasodilator
- B. SUPPORTING/RELATED DOCUMENTS: DMF (b) (4)
(b) (4)
- C. REMARKS: The applicant references the April 5, 2002 submission to DMF (b) (4) in the original submission and the March 14, 2003 submission in new correspondence dated March 18, 2003. In addition, information provided in the August 18, 2003 telephone amendment will also be reviewed (provided in response to a phone mail message not a T-con).

filename: v:microrev\76-582.doc

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** – Not recommended for approval on the basis of sterility assurance
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** –N/A

II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – (b) (4)
- B. **Brief Description of Microbiology Deficiencies** –The DMF is deficient, and the ANDA submission has incomplete information regarding critical operations, endotoxin testing, and environmental monitoring.
- C. **Assessment of Risk Due to Microbiology Deficiencies** -The risk to public health associated with these deficiencies is minimal.

III. Administrative

- A. **Reviewer's Signature** Macla Stevens-Riley
- B. **Endorsement Block**
 M. Stevens-Riley, Ph.D. 10/3/03
 N. J. Sweeney, Ph.D. N. J. Sweeney
 10-3-03
- C. **CC Block**
 cc:
 Original ANDA 76-582
 Division File
 Field Copy

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

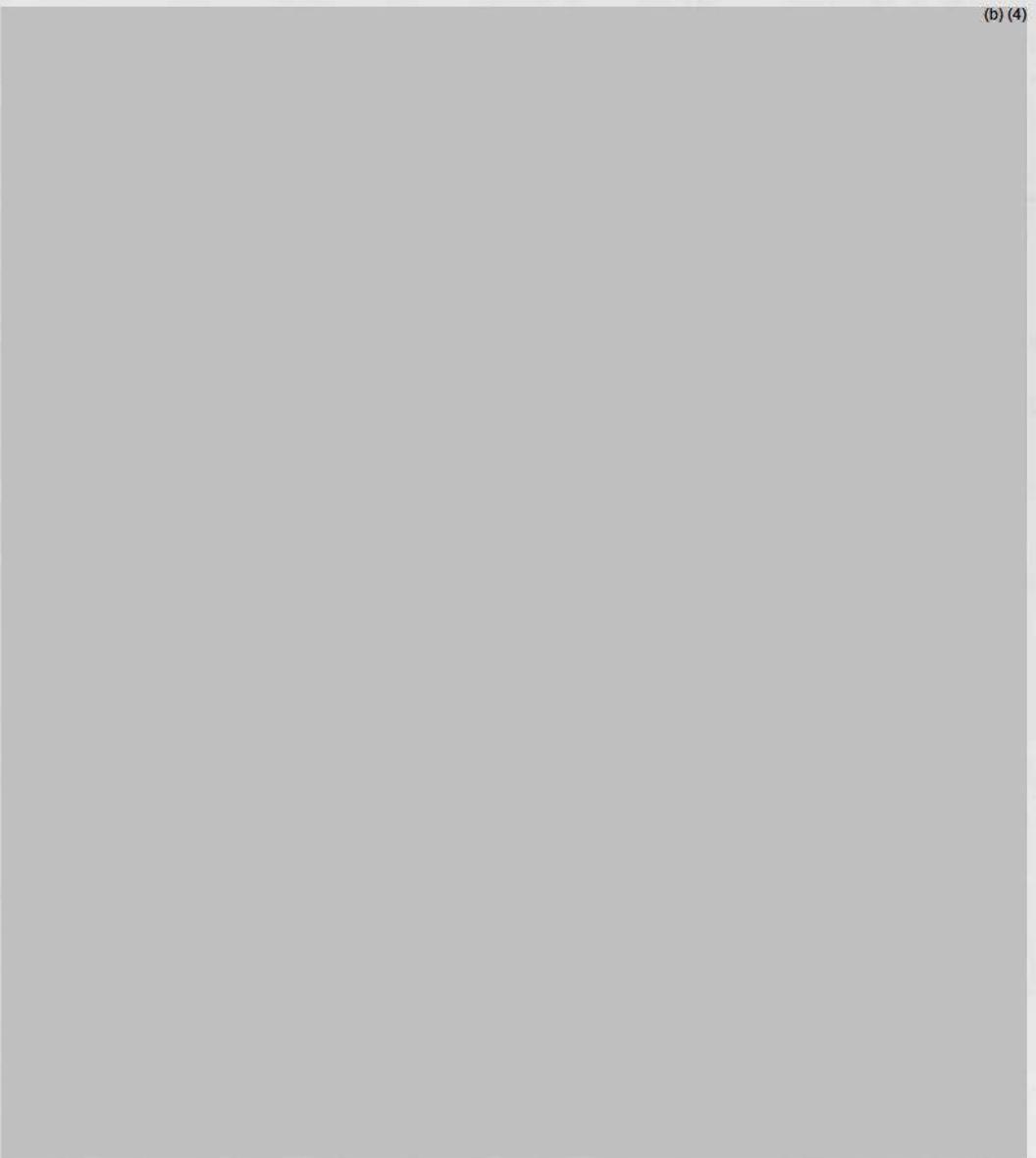
ANDA: 76-582

APPLICANT: Bedford Laboratories

DRUG PRODUCT: Fenoldopam Mesylate Injection USP 10 mg/mL

A. Microbiology Deficiencies:

1. The March 14, 2003 submission to DMF ^{(b) (4)} was reviewed and found inadequate ^{(b) (4)} The DMF holder has been notified.

2.  ^{(b) (4)}

(b) (4)

3.

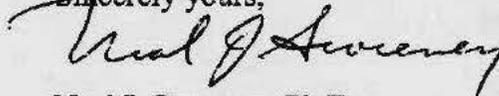
4.

5.

6.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,



Neal J. Sweeney, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 76582

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-582
Drug Product Name	Fenoldopam Mesylate Injection, USP
Strength	10 mg/mL in 1 mL & 2 ml vials
Applicant Name	Bedford Laboratories
Address	Bedford, OH 44146
Submission Date(s)	December 19, 2002
Amendment Date(s)	N.A.
Reviewer	James L. Osterhout
File Location	v:\firmsam\bedford\ltrs&rev\76582W1202.doc

I. Executive Summary

The firm has requested a waiver of *in-vivo* bioequivalence requirements for fenoldopam mesylate injection, USP (10 mg/mL, 1 mL and 2 ml vials). The reference-listed drug (RLD) is Abbott Laboratories Corlopan[®] (10 mg/ml, 1 ml and 2 ml ampules). The firm has submitted comparative formulations of its fenoldopam mesylate injection, USP and Abbott's Corlopan[®] in support of the biowaiver request. The test and RLD products have the same formulation. The biowaiver request is granted based on 21 CFR 320.22(b)(1). This is a first generic.

II. Table of Contents

I. Executive Summary.....	1
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D. <i>In-Vivo</i> Studies.....	2
E. Formulation.....	3
F. In Vitro Dissolution.....	3
G. Waiver Request	3
H. Deficiency Comments.....	3
I. Recommendations.....	3

III. Submission Summary

A. Drug Product Information

Test Product	Fenoldopam Mesylate Injection, USP (10 mg/ml, 1 ml & 2 ml vials)
--------------	---

Reference Product Corloпам - fenoldopam mesylate (10 mg/mL, 1 ml and 2ml ampules), NDA#19922, Abbott Laboratories, Sep 23, 1997

Indication Indicated for short-term (up to 48 hours) in-hospital management of severe hypertension when rapid, but quickly reversible, emergency reduction of blood pressure is clinically indicated.

Relevant DBE History There are no other ANDA's or control documents for this drug product.

B. Contents of Submission

Waiver requests	<input checked="" type="checkbox"/>	How many? 1
-----------------	-------------------------------------	----------------

C. Bioanalytical Method Validation

N/A.

D. *In-Vivo* Studies

N/A.

E. Formulation

The test and reference product formulations are shown below:

Ingredient	IIG	Fenoldopam Mesylate Injection, USP Bedford Laboratories	Corlopan® Fenoldopam Mesylate Injection, USP Abbott Laboratories NDA# 19922, Sep 23, 1997
		10 mg/mL	10 mg/mL
Amount (mg/mL)			
Fenoldopam Mesylate, USP		10 mg base	10 mg base
Sodium Metabisulfite	x	1 mg	1 mg
Citric Acid	x	3.44 mg	3.44 mg
Sodium Citrate	x	0.61 mg	0.61 mg
Propylene Glycol	x	MM (b) (4) 518 mg	418 (b) (4) 518 mg

The formulation was obtained from the Listed Drug Labeling for each product.

Inactive Ingredients within IIG limits
The formulation is acceptable Yes

F. In Vitro Dissolution

N/A

G. Waiver Request

The applicant requests a waiver of in vivo bioequivalence testing under 21 CFR 320.22(b)(1) for the following strength(s): 10 mg/mL, 1 ml & 2 ml vials

H. Deficiency Comments

None

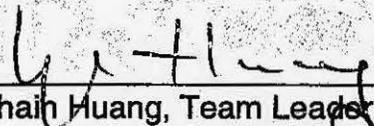
I. Recommendations

The Division of Bioequivalence agrees that the information submitted by Bedford Laboratories demonstrates that its Fenoldopam Mesylate Injection, USP (10 mg/mL, 1 mL & 2 ml vials) falls under the criteria set forth in 21 CFR 320.22(b)(1) of the Bioavailability / Bioequivalence Regulations.

Therefore, the Division of Bioequivalence recommends that a waiver of *in-vivo* bioequivalence study requirements for Fenoldopam Mesylate Injection, USP be

granted. The test product is deemed bioequivalent to Abbott Laboratories Corlopam® (10 mg/mL, 1ml & 2 ml ampules).

 6/18/2003
James L. Osterhout, Reviewer, Review Branch I

 6/18/2003
Yih Chai Huang, Team Leader, Review Branch I

 6/19/03
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

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BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-582

APPLICANT: Bedford Laboratories

DRUG PRODUCT: Fenoldopam Mesylate Injection, USP
(10 mg/mL, 1 mL & 2 ml vials).

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.

Director

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

CC: ANDA 76-582
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ Reviewer J.L. Osterhout
HFD-617/ Project manager A.W. Sigler
HFD-652/ Team Leader Y.C. Huang

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Endorsements: (Final with Dates)

HFD-652/ J.L. Osterhout *JLO 6/18/2003*

HFD-652/ Y.C. Huang *YCH 6/18/2003*

HFD-617/A.W. Sigler

HFD-650/ D.P. Conner *DP 6/19/03*

BIOEQUIVALENCY - ACCEPTABLE

Submission date: December 19, 2002

1. WAIVER (WAI)

olc

Strengths: 10 mg/mL, 1mL & 2 ml vial

Outcome: AC

Outcome Decisions: AC – Acceptable

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 76582

OTHER REVIEWS

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 9, 2004

FROM: Gary Buehler
Director
Office of Generic Drugs
HFD-600

THROUGH: Norman Stockbridge *N. Stockbridge 9/28/04*
Director
Division of Cardio-Renal Drug Products
HFD-110

THROUGH: Rosemary Roberts, M.D. *R. Roberts 9-23-2004*
Director
Office of Counter Terrorism & Pediatric ^{Drug RE} Development
HFD-950

SUBJECT: Pediatric Sections: Proposed Labeling for Generic Corlopadol Drug Products

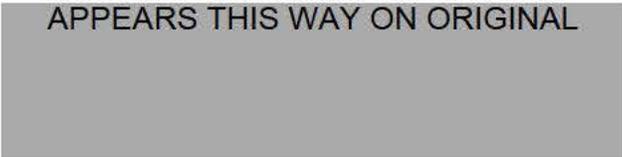
TO: Gary Buehler
Director
Office of Generic Drugs
HFD-600

The Office of Generic Drugs (OGD) consulted this division regarding acceptable package insert labeling for generic Corlopadol (fenoldopam) injection. OGD has asked if the generic firms could carve out information from pediatric studies, without compromising safety or effectiveness for the remainder of the non-exclusivity protected uses. This labeling, which was approved on April 1, 2004, has been granted 3 years of Hatch/Waxman exclusivity. A meeting was held to address this issue on August 4, 2004.

The meeting included representatives from the Division of Cardio-Renal Drug Products, Office of Chief Counsel, Office of Generic Drugs, and the Office of Counter Terrorism & Pediatric Drug Development. The approved pediatric protected additions to the Corlopadol (fenoldopam) labeling, and the proposed generic carve-outs were discussed. The meeting participants reviewed the pertinent sections of the current Corlopadol (fenoldopam) package insert and commented on the impact of each proposed deletion on the safety and effectiveness of the drug product. The conclusion reached was that generic firms **could** carve-out the pediatric labeling sections without rendering generic products less safe or effective for all remaining non-protected conditions of use.

Under the approach proposed by OGD and acceptable to this Division, the Newly Approved sections of the package insert for generic Corlopam (fenoldopam) Injection will have the following changes as presented in the Side-by-Side comparison.

APPEARS THIS WAY ON ORIGINAL



	Approved (4/1/2004)	With Recommended Changes
Third paragraph of the CLINICAL PHARMACOLOGY, Pharmacokinetics	<p>Pediatric Patients: In children, aged 1 month to 12 years old, steady-state fenoldopam plasma concentrations were proportional to dose (0.05 mcg/kg/min to 3.2 mcg/kg/min). The elimination half-life and clearance were 3 to 5 minutes and 3 L/h/kg, respectively.</p> <p>In radiolabeled studies in rats, no more than 0.005% of fenoldopam crossed the blood-brain barrier.</p>	<p>Pediatric Patients: Information related to the pharmacokinetics of fenoldopam injection in pediatric patients is approved for Abbott Laboratories' fenoldopam drug products. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled for pediatric use.</p> <p style="text-align: right;">(b) (4)</p>
CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Studies	<p>Added as the fourth and fifth paragraphs</p> <p>Pediatric Patients: In a randomized, multi-center, double-blind, placebo-controlled, dose-ranging study, pediatric patients were randomized in equal proportions to 1 of 5 treatment groups: 0.05, 0.2, 0.8, or 3.2 mcg/kg/min fenoldopam or placebo. Fenoldopam or placebo was administered as a blinded continuous IV infusion for 30 minutes. Following this, open-label titration of fenoldopam was given to induce hypotension or normotension (defined as mean arterial pressure, MAP, between 50 and 80 mmHg for patients > 1 month of age and MAP between 40 and 70 mmHg for patients ≤ 1 month). Seventy-seven pediatric patients (up to 12 years of age – Tanner Stages 1 and 2) were treated for at least two hours. Of these, 2 were < 1 month of age, 25 were between 1 month of age and 1 year of age, 7 were between 1 and 2 years of age, and 43 were between 2 and 12 years of age. Of the 77 patients enrolled in the trial, 58 were enrolled in association with surgery, and 19 were treated in an ICU setting.</p> <p>The lowest dosage at which decreases in MAP were seen during blinded administration was 0.2 mcg/kg/min. The dose at which the maximum effect was seen was 0.8 mcg/kg/min. Doses higher than 0.8 mcg/kg/min generally produced no further decreases in MAP but did worsen tachycardia (Table 3). Changes in blood pressure and heart rate occurred as early as 5 minutes after starting infusion. Doses as high as 4 mcg/kg/min were administered during the open-label period. The effects increased with time for 15 to 25 minutes, and an effect could still be detected after an average of 4 hours of infusion. When the infusion was discontinued, blood pressure and heart rates approached baseline values during the following 30 minutes.</p>	<p>Pediatric Patients: Information related to the pharmacodynamics and clinical studies of fenoldopam injection in pediatric patients is approved for Abbott Laboratories' fenoldopam drug products. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled for pediatric use.</p>

Approved (4/1/2004)

With Recommended Changes

Table 3
PHARMACODYNAMIC EFFECTS OF FENOLDOPAM IN PEDIATRIC PATIENTS
Baseline Mean and Mean Change ± SE

	Drug Dosage (mcg/kg/min)				
	Placebo	0.05	0.2	0.8	3.2
	n = 16	n = 15*	n = 16	n = 15	n = 15
Pre-Infusion Baseline					
Mean Arterial Pressure	81 ± 4	77 ± 5	76 ± 4	88 ± 6	74 ± 4
Systolic BP	108 ± 5	103 ± 6	104 ± 6	117 ± 7	98 ± 4
Diastolic BP	62 ± 4	61 ± 4	57 ± 3	69 ± 6	56 ± 3
Heart rate	106 ± 8	110 ± 7	119 ± 7	125 ± 6	122 ± 6
Change at 5 Minutes of Infusion					
Mean Arterial Pressure	4 ± 2	3 ± 3	-2 ± 2	-3 ± 3	-6 ± 3
Systolic BP	5 ± 3	3 ± 3	-2 ± 3	-5 ± 3	-8 ± 3
Diastolic BP	4 ± 2	6 ± 2	-1 ± 2	-2 ± 2	-4 ± 2
Heart rate	2 ± 3	-2 ± 3	-1 ± 3	4 ± 3	-2 ± 3
Change at 30 Minutes of Infusion (LOCF§)					
Mean Arterial Pressure	0 ± 3	-1 ± 3	-2 ± 3	-10 ± 3	-10 ± 3
Systolic BP	-3 ± 4	0 ± 4	-3 ± 4	-12 ± 4	-10 ± 4
Diastolic BP	0 ± 3	1 ± 3	-2 ± 3	-8 ± 3	-6 ± 3
Heart rate	-6 ± 4	-4 ± 4	5 ± 4	7 ± 4	14 ± 4

* For Mean Arterial Pressure, n=14; otherwise, n=15.
 § Dropouts were accounted for using the Last Observation Carried Forward (LOCF) method of analysis.

Continued from section above:

At end of the CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Studies

INDICATIONS AND USAGE

Adult Patients: Fenoldopam is indicated for the in-hospital, short-term (up to 48 hours) management of severe hypertension when rapid, but quickly reversible, emergency reduction of blood pressure is clinically indicated, including malignant hypertension with deteriorating end-organ function. Transition to oral therapy with another agent can begin at any time after blood pressure is stable during fenoldopam infusion.

Pediatric Patients: Fenoldopam is indicated for the in-hospital, short-term (up to 4 hours) reduction in blood pressure (See CLINICAL PHARMACOLOGY/Pediatric Patients).

Adult Patients: Fenoldopam is indicated for the in-hospital, short-term (up to 48 hours) management of severe hypertension when rapid, but quickly reversible, emergency reduction of blood pressure is clinically indicated, including malignant hypertension with deteriorating end-organ function. Transition to oral therapy with another agent can begin at any time after blood pressure is stable during fenoldopam infusion.

Pediatric Patients: Information related to the indicated use of fenoldopam injection in pediatric patients is approved for Abbott Laboratories' fenoldopam drug products. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled for pediatric use.

	Approved (4/1/2004)	With Recommended Changes
Last sentence PRECAUTIONS, Tachycardia	Tachycardia in adults diminishes over time but remains substantial at higher doses. Tachycardia in pediatric patients at doses > 0.8 mcg/kg/min persists at least for 4 hours.	Tachycardia in adults diminishes over time but remains substantial at higher doses. Tachycardia in pediatric patients at doses > 0.8 mcg/kg/min persists at least for 4 hours. (Decided to leave in as of the 8/4/04 meeting with the Ped. division)
End of PRECAUTIONS, Hypotension	In pediatric patients, fenoldopam was only administered to patients with an indwelling intraarterial line.	In pediatric patients, fenoldopam was only administered to patients with an indwelling intraarterial line.
PRECAUTIONS/Pediatric Use	Anti-hypertensive effects of fenoldopam have been studied in pediatric patients age <1 month (at least 2 kg or full term) to 12 years old requiring blood pressure reduction (see Pharmacodynamics and Clinical Studies, Pediatric Patients). Clinical studies of fenoldopam did not include subjects ages 12 to 16 years of age to determine if they respond differently from younger subjects or adults. The pharmacokinetics of fenoldopam are independent of age when corrected for body weight. Dose selection for patients 12 to 16 years of age should consider the patient's clinical condition and concomitant drug therapy.	Clinical study information related to the safety and effectiveness of fenoldopam injection in pediatric patients age <1 month to 12 years old is approved for Abbott Laboratories' fenoldopam drug products. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled for pediatric use.
End of ADVERSE REACTIONS	Pediatric Patients: In pediatric patients, the most common adverse events reported during short term administration in controlled trials (30 minutes) were hypotension and tachycardia. However, because of the short exposure, there is limited experience with defining adverse events in children. The long-term effects of fenoldopam on growth and development have not been studied.	Pediatric Patients: Information relating to treatment-emergent adverse events is approved for Abbott Laboratories' fenoldopam injection drug products. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled for pediatric use.

Approved (4/1/2004)

With Recommended Changes

Table 5
FENOLDOPAM ADULT INFUSION RATES (mL/hour)
DRUG DOSAGE FOR ADULTS > 40 KG, USING 40 MCG/ML CONCENTRATION
NOTE: CONCENTRATION IS DIFFERENT FROM PEDIATRIC PATIENTS, TABLE 6.

Body Weight (kg)	Infusion Rate				
	0.025	0.05	0.1	0.2	0.3
	mcg/kg/min n	mcg/kg/min n	mcg/kg/min	mcg/kg/min n	mcg/kg/min n
Infusion Rates (mL/hour) of 40 mcg/mL solution					
40	1.5	3	6	12	18
50	1.9	3.8	7.5	15	22.5
60	2.3	4.5	9.0	18	27
70	2.6	5.3	10.5	21	31.5
80	3	6	12	24	36
90	3.4	6.8	13.5	27	40.5
100	3.8	7.5	15	30	45
110	4.1	8.3	16.5	33	49.5
120	4.5	9	18	36	54
130	4.9	9.8	19.5	39	58.5
140	5.3	10.5	21	42	63
150	5.6	11.3	22.5	45	67.5

Table 5 (continued)
FENOLDOPAM ADULT INFUSION RATES (mL/hour)
DRUG DOSAGE FOR ADULTS > 40 KG, USING 40 MCG/ML CONCENTRATION
NOTE: CONCENTRATION IS DIFFERENT FROM PEDIATRIC PATIENTS, TABLE 6.

Body Weight (kg)	Infusion Rate					
	0.5	0.8	1	1.2	1.4	1.6
	mcg/kg/min n	mcg/kg/min n	mcg/kg/min n	mcg/kg/min n	mcg/kg/min n	mcg/kg/min n
Infusion Rates (mL/hour) of 40 mcg/mL solution						
40	30	48	60	72	84	96
50	37.5	60	75	90	105	120
60	45	72	90	108	126	144
70	52.5	84	105	126	147	168
80	60	96	120	144	168	192
90	67.5	108	135	162	189	216
100	75	120	150	180	210	240
110	82.5	132	165	198	231	264
120	90	144	180	216	252	288
130	97.5	156	195	234	273	312
140	105	168	210	252	294	336
150	112.5	180	225	270	315	360

DOSAGE AND ADMINISTRATION

Table 5

Same as approved Table 5 with the exception of the following information in the heading of the table:

FENOLDOPAM ADULT INFUSION RATES (mL/hour)
DRUG DOSAGE FOR ADULTS > 40 KG, USING 40 MCG/ML CONCENTRATION

NOTE: CONCENTRATION IS DIFFERENT FROM PEDIATRIC PATIENTS, (See below: Pediatric Patients).

Approved (4/1/2004)

With Recommended Changes

End of DOSAGE AND ADMINISTRATION

Pediatric Patients:

Fenoldopam should be administered intravenously to pediatric patients by a continuous infusion pump appropriate for the delivery of low infusion rates. Monitoring of blood pressure should be continuous, usually by way of an intra-arterial line. Heart rate should also be continuously monitored. In the clinical trial, the usual starting dose was 0.2 mcg/kg/min with an effect on MAP evident within 5 minutes. At a constant infusion rate the effect was maximal after 20 to 25 minutes. Increased dosages of up to 0.3 to 0.5 mcg/kg/min every 20 to 30 minutes were generally well tolerated. Tachycardia without further decrease in MAP occurred at dosages greater than 0.8 mcg/kg/min. Upon discontinuation of the fenoldopam infusion after an average of 4 hours of therapy, blood pressure and heart rate returned to near baseline within 30 minutes.

PREPARATION OF INFUSION SOLUTION

WARNING: CONTENTS OF AMPULES MUST BE DILUTED BEFORE INFUSION. EACH AMPULE IS FOR SINGLE USE ONLY.

Dilution:

Pediatric Patients:

mL of Concentrate (mg of drug)	Added to	Final Concentration
3 mL (30 mg)	500 mL	60 mcg/mL
1.5 mL (15 mg)	250 mL	60 mcg/mL
0.6 mL (6 mg)	100 mL	60 mcg/mL

Table 6 provides the calculated infusion volume in mL/hour for a range of drug doses and body weights. The infusion should be administered using a calibrated mechanical infusion pump that can accurately and reliably deliver the desired infusion rate. As low flow rates (e.g., <0.5 mL/hr) may not be practical, and due to volume overload, it may be necessary to increase the concentration of fenoldopam in the infused solutions.

Pediatric Patients: Information related to the dosing and administration of fenoldopam injection in pediatric patients is approved for Abbott Laboratories' fenoldopam drug products. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled for pediatric use.

	Approved (4/1/2004)	With Recommended Changes																																																					
End of DOSAGE AND ADMINISTRATION	<p>Infusion Rates:</p> <p style="text-align: center;">Table 6 FENOLDOPAM PEDIATRIC INFUSION RATES (mL/hour) DRUG DOSAGE FOR CHILDREN BETWEEN 5 AND 70 KG, USING 60 MCG/ML CONCENTRATION</p> <p>NOTE: CONCENTRATION IS DIFFERENT FROM ADULT PATIENTS, TABLE 5.</p>																																																						
	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th rowspan="2" style="text-align: center;">Body Weight (kg)</th> <th colspan="5" style="text-align: center;">Infusion Rate</th> </tr> <tr> <th style="text-align: center;">0.2 mcg/kg/min</th> <th style="text-align: center;">0.5 mcg/kg/min</th> <th style="text-align: center;">0.8 mcg/kg/min</th> <th style="text-align: center;">1 mcg/kg/min</th> <th style="text-align: center;">1.2 mcg/kg/min</th> </tr> </thead> </table>		Body Weight (kg)	Infusion Rate					0.2 mcg/kg/min	0.5 mcg/kg/min	0.8 mcg/kg/min	1 mcg/kg/min	1.2 mcg/kg/min																																										
	Body Weight (kg)	Infusion Rate																																																					
		0.2 mcg/kg/min	0.5 mcg/kg/min	0.8 mcg/kg/min	1 mcg/kg/min	1.2 mcg/kg/min																																																	
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="6" style="text-align: center;">Infusion Rates (mL/hr) of 60 mcg/mL solution</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">5</td> <td style="text-align: center;">1</td> <td style="text-align: center;">2.5</td> <td style="text-align: center;">4</td> <td style="text-align: center;">5</td> <td style="text-align: center;">6</td> </tr> <tr> <td style="text-align: center;">10</td> <td style="text-align: center;">2</td> <td style="text-align: center;">5</td> <td style="text-align: center;">8</td> <td style="text-align: center;">10</td> <td style="text-align: center;">12</td> </tr> <tr> <td style="text-align: center;">20</td> <td style="text-align: center;">4</td> <td style="text-align: center;">10</td> <td style="text-align: center;">16</td> <td style="text-align: center;">20</td> <td style="text-align: center;">24</td> </tr> <tr> <td style="text-align: center;">30</td> <td style="text-align: center;">6</td> <td style="text-align: center;">15</td> <td style="text-align: center;">24</td> <td style="text-align: center;">30</td> <td style="text-align: center;">36</td> </tr> <tr> <td style="text-align: center;">40</td> <td style="text-align: center;">8</td> <td style="text-align: center;">20</td> <td style="text-align: center;">32</td> <td style="text-align: center;">40</td> <td style="text-align: center;">48</td> </tr> <tr> <td style="text-align: center;">50</td> <td style="text-align: center;">10</td> <td style="text-align: center;">25</td> <td style="text-align: center;">40</td> <td style="text-align: center;">50</td> <td style="text-align: center;">60</td> </tr> <tr> <td style="text-align: center;">60</td> <td style="text-align: center;">12</td> <td style="text-align: center;">30</td> <td style="text-align: center;">48</td> <td style="text-align: center;">60</td> <td style="text-align: center;">72</td> </tr> <tr> <td style="text-align: center;">70</td> <td style="text-align: center;">14</td> <td style="text-align: center;">35</td> <td style="text-align: center;">56</td> <td style="text-align: center;">70</td> <td style="text-align: center;">84</td> </tr> </tbody> </table>		Infusion Rates (mL/hr) of 60 mcg/mL solution						5	1	2.5	4	5	6	10	2	5	8	10	12	20	4	10	16	20	24	30	6	15	24	30	36	40	8	20	32	40	48	50	10	25	40	50	60	60	12	30	48	60	72	70	14	35	56	70	84
Infusion Rates (mL/hr) of 60 mcg/mL solution																																																							
5	1	2.5	4	5	6																																																		
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60	12	30	48	60	72																																																		
70	14	35	56	70	84																																																		
<p>The diluted solution is stable under normal ambient light and temperature conditions for at least 24 hours. Diluted solution that is not used within 24 hours of preparation should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter or cloudiness is observed, the drug should be discarded.</p>																																																							
<p>Pediatric Patients: Information related to the dosing and administration of fenoldopam injection in pediatric patients is approved for Abbott Laboratories' fenoldopam drug products. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled for pediatric use.</p>																																																							

The Division of Cardio-Renal Drug Products believes that generic Corlopam (fenoldopam) injection applications can be approved without including the pediatric use sections in the labeling. Omitting the protected text, as indicated above, will not render the generic products less safe or effective than the listed drug(s) for all remaining non-protected conditions of use.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 76582

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-582

Applicant Bedford Laboratories

Drug Fenoldopam Mesylate Unjection USP

Strength(s) 10 mg (base)/mL, Packaged in 10 mg (base)/1 mL and 20 mg (base)/2 mL single-dose vials.

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER:

DRAFT Package

FINAL Package

1. Martin Shimer
Chief, Reg. Support Branch

Date 27 Aug 04
Initials MS

Date 10/20/04
Initials MS

Contains GDEA certification: Yes No Determ. of Involvement? Yes No
(required if sub after 6/1/92) Pediatric Exclusivity System

Patent/Exclusivity Certification: Yes No RLD = NDA# 19-922
If Para. IV Certification- did applicant Date Checked 10/10/04

Notify patent holder/NDA holder Yes No Nothing Submitted

Was applicant sued w/in 45 days: Yes No Written request issued

Has case been settled: Yes No Study Submitted

Is applicant eligible for 180 day Date settled:

Generic Drugs Exclusivity for each strength: Yes No

Date of latest Labeling Review/Approval Summary 8/2/04

Any filing status changes requiring addition Labeling Review Yes No

Type of Letter: Full approval I was being covered out per previous recommendations

Comments:

2. Project Manager, Wanda Pamphile Team 5
Review Support Branch

Date 8/27/04
Initials WP

Date _____
Initials _____

Original Rec'd date 12-18-02 EER Status Pending Acceptable OAI

Date Acceptable for Filing 12-19-02 Date of EER Status 8-4-03

Patent Certification (type) I Date of Office Bio Review 10-19-03

Date Patent/Exclus. expires N/A Date of Labeling Approv. Sum 8/27/04

Citizens' Petition/Legal Case Yes No Labeling Acceptable Email Rec'd Yes No

(If YES, attach email from PM to CP coord) Labeling Acceptable Email filed Yes No

First Generic Yes No Date of Sterility Assur. App. 2-17-04

Methods Val. Samples Pending Yes No

MV Commitment Rcd. from Firm Yes No

Acceptable Bio reviews tabbed Yes No Modified-release dosage form: Yes No

Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes

Pediatric Waiver Request Accepted Rejected Pending

Previously reviewed and tentatively approved Date 4-20-04 AE letter

Previously reviewed and CGMP def. /NA Minor issued Date _____

Comments:

3. David Read (PP IVs Only) Pre-MMA Language included

Date _____
Initials _____

OGD Regulatory Counsel, Post-MMA Language Included

Comments:

N/A

4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III

Date 10/8/04
Initials RCG

Comments:

The emc is satisfactory for AF

REVIEWER:

FINAL ACTION

5. Frank Holcombe First Generics Only
Assoc. Dir. For Chemistry

Date _____
Initials _____

Comments: (First generic drug review)

N/A. ANDA 76-656 submitted by PharmaFACE, Inc. for this drug product was approved on 12/1/03. This ANDA received an Approvable letter pending resolution of BPCA "carve-out" on 4/20/04.

6. Vacant
Deputy Dir. DLPS

Date _____
Initials _____

RD = Corolopam Injection 10mg/5ml
Abbott Laboratories NDA 19-922
Hospira

7. Peter Rickman
Director, DLPS

Date 10/26/04
Initials PR

Para. IV Patent Cert: Yes No Pending Legal Action: Yes No Petition: Yes No

Comments: Acceptable EES dated 8/4/03 verified 10/12/04. No OAI alerts noted.

Refer to the sign-off form completed at the time of issuance of the approvable letter to Bedford on 4/20/04. On 7/1/04 Bedford submitted revised FPL and requested final approval for the ANDA. The FPL was amended on 8/12/04 to reflect the "pediatric carve-out" under BPCA. A memorandum dated 1/04 was endorsed by both representatives from OIM/HFD-110 and the PETS Team concluding that the "carve-out" was acceptable. FPL found acceptable 8/26/04. CHC found acceptable for approval 10/8/04. Methods validation is not required - both the API and drug product are

8. Robert L. West
Deputy Director, OGD

Date _____
Initials _____

Para. IV Patent Cert: Yes No Pending Legal Action: Yes No Petition: Yes No

Comments: Bedford has addressed Abbott's/Hospira's E-422 pediatric use exclusivity via "carve-out" under BPCA.

This ANDA is recommended for approval.

9. Gary Buehler
Director, OGD

Date 10/26/04
Initials RB

Comments:
First Generic Approval PD or Clinical for BE Special Scientific or Reg. Issue

10. Project Manager, Team Wanda Pamphile

Date 10/12/04
Initials WP

Review Support Branch 5
Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

1:24 Time notified of approval by phone 1:39 Time approval letter faxed

FDA Notification:

10/12/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

10/26/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-582

Applicant Bedford Laboratories

Drug Fenoldopam Mesylate Injection, USP Strength(s) 10 mg (base)/mL, packaged in 10 mg (base) 1 mL and 20 mg (base)/2 mL single-dose ampoules vials

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER:

DRAFT Package

FINAL Package

1. Martin Shimer
Chief, Reg. Support Branch

Date 12 April 2004
Initials MS

Date _____
Initials _____

Contains GDEA certification: Yes No Determ. of Involvement? Yes No
(required if sub after 6/1/92) Pediatric Exclusivity System

Patent/Exclusivity Certification: Yes No

RLD = _____ NDA# _____

Date Checked _____

If Para. IV Certification- did applicant

Nothing Submitted

Notify patent holder/NDA holder Yes No

Written request issued

Was applicant sued w/in 45 days: Yes No

Study Submitted

Has case been settled: Yes No

Date settled: _____

Is applicant eligible for 180 day

Generic Drugs Exclusivity for each strength: Yes No

Type of Letter: _____

Comments: _____

NO patents/exclusivity eligible for (FA) upon resolution of outstanding labeling issue.

2. Project Manager, Wanda Pamphile Team 5
Review Support Branch

Date 4/12/04
Initials WP

Date _____
Initials _____

Original Rec'd date 12-18-02
Date Acceptable for Filing 12-19-02 ✓
Patent Certification (type) I
Date Patent/Exclus. expires N/A

EER Status Pending Acceptable OAI
Date of EER Status 8-4-03
Date of Office Bio Review 6-19-03
Date of Labeling Approv. Sum _____

Citizens' Petition/Legal Case Yes No
(If YES, attach email from PM to CP coord)

Date of Sterility Assur. App. 2-17-04
Methods Val. Samples Pending Yes No

First Generic Yes No

MV Commitment Rcd. from Firm Yes No

Acceptable Bio reviews tabbed Yes No

Modified-release dosage form: Yes No

Suitability Petition/Pediatric Waiver

Interim Dissol. Specs in AP Ltr: Yes

Pediatric Waiver Request Accepted Rejected Pending

Previously reviewed and tentatively approved Date _____

Previously reviewed and CGMP def./NA Minor issued Date _____

Comments: _____

3. Div. Dir./~~Deputy Dir.~~
Chemistry Div. I ~~or~~ II
Comments: _____

Date 4/19/04
Initials RC

AE from comc perspective; pending is a labeling issue to be resolved @ Abbott (RLD)

4. Frank Holcombe First Generics Only
Assoc. Dir. For Chemistry
Comments: (First generic drug review)

Date _____
Initials _____

N/A. ANDA 76-656 (Pharmacia) for this drug product was approved on 12/1/03.

REVIEWER:

FINAL ACTION

5. Gregg Davis
Deputy Dir., DLPS

Date _____
Initials _____

RID = Corlopam[®] Injection 10mg (base)/mL
Abbott Laboratories (Hospital Products Division)

NDA 19-922

There are no unexpired patents currently listed in the Orange Book for this drug product. However, on 4/1/04 new labeling was approved for Abbott's Corlopam Injection which is protected by Waxman/Hatch exclusivity (3 years).

6. Peter Rickman
Director, DLPS

Date 4/20/04
Initials [Signature]

Para. IV Patent Cert: Yes No Pending Legal Action: Yes No Petition: Yes No

Comments: Acceptable EES dated 8/4/03 (Verified 4/20/04). No D.A.I. alerts noted. BDE equivalence waiver granted under 21CFR 320.22(b)(1). The drug product is "AND" to the RID. Office level bio endorsed 6/9/03. Microbiology/sterility assurance found acceptable 2/7/04. CMC found acceptable 4/15/04. Methods Validation is not required both the API and the drug product are compendial. Labeling is pending "carve out" of pediatric labeling approved for Abbott on 4/1/04.

6. Robert L. West
Deputy Director, OGD

Date 4/20/2004
Initials [Signature]

Para. IV Patent Cert: Yes No Pending Legal Action: Yes No Petition: Yes No

Comments: On 4/1/04, the new drug review division approved new labeling for Abbott's Corlopam Injection. This new labeling will be granted 3 years of H/W exclusivity and provides for the use of Corlopam Injections for the use of short-term (up to 4 hours) reductions in blood pressure in pediatric patients. Our labeling group is currently in the process of "carving-out" the protected information as permitted under the BPCA.

Plan: Issue an approvable letter to Bedford. The ANDA may be approved when the "carve-out" process has been completed and FPL has been submitted and found acceptable.

7. Gary Buehler
Director, OGD

Date 4/20/04
Initials GB

Comments: First Generic Approval PD or Clinical for BE Special Scientific or Reg. Issue

8. Project Manager, Team Wanda Pamphile
Review Support Branch 5

Date 4/20/04
Initials [Signature]

Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
9:55 Time notified of approval by phone 10:00 Time approval letter faxed
FDA Notification:
4/20/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
4/20/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

APR 20 2004

Bedford Laboratories
Attention: Molly L. Rapp
300 Northfield Road
Bedford, OH 44146

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 18, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fenoldopam Mesylate Injection USP, 10 mg (base)/mL, packaged in 10 mg (base)/1 mL and 20 mg (base)/2 mL single-dose vials.

Reference is also made to your amendments dated August 18, and November 14, 2003; and February 3, and March 19, 2004.

We have completed the review of this ANDA as submitted, and have concluded that the application is **approvable**. We are unable to grant final approval to your application at this time because certain portions of the approved labeling for the reference listed drug product, Corlopan[®] Injection of Abbott Laboratories, is subject to a period of exclusivity. This exclusivity was granted by the Agency in response to the approval on April 4, 2004, of Abbott's supplemental application providing for the use of Corlopan[®] Injection in a pediatric population. However, the Best Pharmaceuticals for Children Act (BPCA) signed into law in January 2002 allows certain portions of Abbott's approved labeling pertaining to the use of the drug product in a pediatric population to be omitted from the labeling of products approved under Section 505(j). The BPCA also permits the addition of language to the labeling of products approved under Section 505(j) that informs health care practitioners that Abbott's drug product has been approved for pediatric use. Thus, before your application may receive final approval, the Agency must agree on appropriate labeling under BPCA that will provide assurance that your product can be used safely and effectively and that addresses Abbott's exclusivity. This process is currently ongoing.

The Agency expects to complete its review of this regulatory issue as promptly as possible. You will be notified promptly when the Agency has resolved the pending regulatory issues and you will be provided a copy of a template which the Agency has decided represents an acceptable template for the labeling for Fenoldopam Mesylate Injection, USP under BPCA. You will be requested to submit revised final-printed package insert labeling at that time. There is no additional material that you should submit to the Agency at this time to obtain final approval of your ANDA. Please note that the disposition of this issue could affect the final approval decision for your ANDA.

Any significant changes in the conditions outlined in your abbreviated new drug application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to Agency review before final approval of the application will be made.

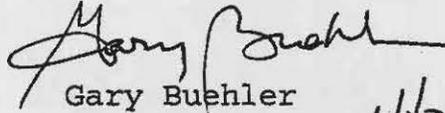
This is not an approval letter. This drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 301(d) of the Act. Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under Section 505 of the Act and will not be listed in "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), published by the Agency.

A copy of the approved package insert for Corlopam[®] Injection USP, 10 mg (base)/mL is available on the FDA Website at http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html.

Please contact Jim Barlow, R.Ph., of our labeling review group if you have further questions concerning the proposed labeling for the product.

You may also contact Wanda Pamphile, Pharm.D., Project Manager,
(301) 827-5763 if you have further questions regarding the
status of your application.

Sincerely yours,



Gary Buehler
Director

4/20/04

Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-582
Division File
Field Copy
GCF-1 Liz Dickinson
HFD-610/R.West
HFD-330

Endorsements:

HFD-645/B.Cai
HFD-647/S.Liu S.H. Liu 4/15/04
HFD-617/W.Pamphile 4/15/04
HFD-613/J.Barlow
HFD-613/J.Grace

AE
REC'd
4/19/04

V:\FIRMSAM\BEDFORD\LTRS&REV\76582.approvable.doc

APPROVABLE LETTER

Robert West
4/20/2004

Pamphile, Wanda

From: West, Robert L
Sent: Friday, April 09, 2004 6:46 AM
To: Pamphile, Wanda
Subject: RE: Corlopam (fenoldopam mesylate) approved for new ped use

Yes. Essentially, the approvable letter is reserved by OGD for those times when the labeling is still up in the air.

Thanks,

Bob

-----Original Message-----

From: Pamphile, Wanda
Sent: Thursday, April 08, 2004 3:46 PM
To: West, Robert L
Subject: RE: Corlopam (fenoldopam mesylate) approved for new ped use

Can we still issue an approvable letter without a labeling AP summary?

-----Original Message-----

From: West, Robert L
Sent: Thursday, April 08, 2004 3:26 PM
To: Pamphile, Wanda
Cc: Ames, Timothy W
Subject: FW: Corlopam (fenoldopam mesylate) approved for new ped use

Wanda:

F.Y.I. Regarding ANDA 76-582 for Bedford's ANDA. Please change the approval letter to an approvable letter pending the agency's resolution of labeling.

See the attachment to my message below. It is an example of an approvable letter we recently issued for Ribavirin Capsules where labeling issues were still unresolved.

We should still get this one out this month.

<< File: 76203.approvable.doc >>

Thanks,

Bob

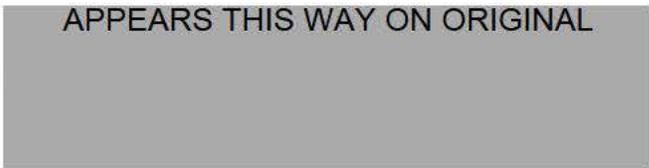
-----Original Message-----

From: Grace, John F
Sent: Thursday, April 08, 2004 10:59 AM
To: Rickman, William P
Cc: West, Robert L; Ames, Timothy W; Buehler, Gary J; Barlow, James T; Eng, Simon
Subject: Corlopam (fenoldopam mesylate) approved for new ped use

Approved 4/1/2004 for the use of Corlopam (fenoldopam mesylate) 10mg/mL Injection for the in-hospital, short-term (up to 4 hours) reduction in blood pressure in pediatric patients.

The exclusivity checklist recommends 3 years WH exclus. We are starting the BPCA consult process now
<< File: corlopam >> << File: exclusivity checklist >>

APPEARS THIS WAY ON ORIGINAL



Pamphile, Wanda

From: Grace, John F
Sent: Thursday, April 08, 2004 5:24 PM
To: 'Benyo, Laurel BVL-US-B'; Grace, John F; Barlow, James T
Cc: Rapp, Molly BVL-US-B; Pamphile, Wanda; Usrey, Beth BVL-US-B
Subject: RE: Fenoldopam 76-582

correct we will advise on the language throughout labeling

-----Original Message-----

From: Benyo, Laurel BVL-US-B [mailto:LBenyo@cle.boehringer-ingenelheim.com]
Sent: Thursday, April 08, 2004 5:17 PM
To: 'Grace, John F'; Benyo, Laurel BVL-US-B; Barlow, James T
Cc: Rapp, Molly BVL-US-B; Pamphile, Wanda; Usrey, Beth BVL-US-B
Subject: RE: Fenoldopam 76-582

So I need to wait for the Center to advise me what the new language should be, is that correct?

Sorry to appear so confused

Laurel Benyo
Regulatory Affairs Labeling Associate
Ben Venue Laboratories, Inc.
300 Northfield Rd.
Bedford, OH 44146
Direct Phone 440-201-3293
Fax Number 440-232-2772
Email "lbenyo@cle.boehringer-ingenelheim.com"

-----Original Message-----

From: Grace, John F [mailto:GRACEJ@cder.fda.gov]
Sent: Thursday, April 08, 2004 4:58 PM
To: 'Benyo, Laurel BVL-US-B'; Grace, John F; Barlow, James T
Cc: Rapp, Molly BVL-US-B; Pamphile, Wanda; Usrey, Beth BVL-US-B
Subject: RE: Fenoldopam 76-582

Don't revise your labeling yet. That new language is protected for 3 years

-----Original Message-----

From: Benyo, Laurel BVL-US-B [mailto:LBenyo@cle.boehringer-ingenelheim.com]
Sent: Thursday, April 08, 2004 4:56 PM
To: 'Grace, John F'; Benyo, Laurel BVL-US-B; Barlow, James T
Cc: Rapp, Molly BVL-US-B; Pamphile, Wanda; Usrey, Beth BVL-US-B
Subject: Fenoldopam 76-582

Mr Grace and Mr. Barlow:

Sorry, I overlooked the Precautions section in my enthusiasm. You are absolutely correct, I will make the changes to the Pediatric Use subsection and submit new final printed labeling samples. Naturally, we will also use these new inserts in our launch batch. As mentioned earlier in a telephone conversation with Mr. Barlow, we packaged these "at risk" and the agency was understanding enough to allow us to launch one lot before correcting the labels and cartons. We will, of course, remove the incorrect insert and replace with the revised Precautions prior to launching any product.

Thank you for helping me out. Final printed labeling samples will be sent for review early next week.

Laurel Benyo
Regulatory Affairs Labeling Associate
Ben Venue Laboratories, Inc.
300 Northfield Rd.
Bedford, OH 44146
Direct Phone 440-201-3293
Fax Number 440-232-2772
Email "lbenyo@cle.boehringer-ingenelheim.com"



(b) (4)

Memorandum to the File

ANDA: 76-582

DRUG: Fenoldopam Mesylate Injection USP,
10 mg/mL, 1 mL and 2 mL vials

SUBJECT: Clarification of error on Microbiology Deficiencies Fax
Cover sheet sent to firm on October 10, 2003.

FIRM: Bedford Laboratories, Inc.

DATE: October 29, 2003

Please note that the fax cover sheet sent to the firm with Microbiology deficiencies contained errors. The fax sheet stated that the file on the application was closed with the issuing of these Microbiology deficiencies. **This is incorrect.** Only the issuance of Chemistry deficiencies can close the file on an application.

Therefore this memo should correct the file and clarify that the cover sheet was sent to the firm in error, and the file on this application should not be closed with the issuance of these deficiencies.

In the future a corrected cover sheet will be used to issue Microbiology deficiencies.

My apologies to the Document Room staff for this oversight.

Bonnie McNeal 10/29/03

Bonnie McNeal
Project Manager, Microbiology Team, OGD

cc: ANDA 76-582 ✓
Division file
HFD-617/TAmes

File: V:\FIRMSAM\Bedford\MEMOS\76582Micro.doc

MAY 29 2003

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-582

APPLICANT:

Bedford Laboratories

DRUG PRODUCT: Fenoldopam Mesylate Injection USP 10 mg/mL, 1 mL and 2 mL vials

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File No. (b)(4) has been found deficient. We have notified the DMF holder, (b)(4) of the deficiencies. Please do not respond to this deficiency letter until the DMF holder submits a complete response to the Agency.

2.

3.

4.

5.

6.

7.

(b)(4)

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:
1. Please provide all available long-term drug product stability data (samples stored at conditions of room temperature and 2-8°C).
 2. Your labeling information is found deficient. Labeling deficiencies also need to be addressed in your reply.
 3. Your bioequivalence information and sterility assurance are pending review. Deficiencies, if any, will be communicated separately.
 4. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.
 5.  (b) (4)

Sincerely yours,



Rashmikant M. Patel, Ph.D.

Director

Division of Chemistry I

Office of Generic Drugs

Center for Drug Evaluation and Research

**ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION**

ANDA# 76-582

FIRM NAME BEDFORD LABORATORIES

RELATED APPLICATION(S) NA FIRST GENERIC? YES

DRUG NAME: FENOLDOPAM MESYLATE

DOSAGE FORM: INJECTION USP, 10 MG/ML 1 ML AND 2 ML VIALS

Electronic Submission: NA E-mail notification sent: NA Comments: NA

Random Assignment Queue: Random I Chem Team Leader: Mueller, Al PM: Keister, Craig

Labeling Reviewer: Barlow, Jim Micro Review: YES PD study (Med Ofcr): NA

Letter Date	DECEMBER 18, 2002	Received Date	DECEMBER 19, 2002
Comments EC 1	YES	On Cards	YES
HYPERTENSIVE AGENTS		Therapeutic Code	1020100 ANTI-
Methods Validation Package (3 copies)	<i>USP Drug</i>		
(Required for Non-USP drugs)			
Archival, and Review copies			
Field Copy Certification (Original Signature)	YES		
Cover Letter	YES		
Table of Contents	YES		

ACCEPTABLE

Sec. I	Signed and Completed Application Form (356h) (Statement regarding Rx/OTC Status) RX YES	<input checked="" type="checkbox"/>
Sec. II	Basis for Submission NDA: 19-922 RLD: CORLOPAM Firm: ABBOTT ANDA suitability petition required? If yes, consult needed for pediatric study requirement.	<input checked="" type="checkbox"/>
Sec. III	Patent Certification 1. Paragraph: I 2. Expiration of Patent: A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? Exclusivity Statement YES NCE SEPTEMBER 23, 2002	<input checked="" type="checkbox"/>

<p>Sec. IV</p>	<p>Comparison between Generic Drug and RLD-505(j)(2)(A)</p> <ol style="list-style-type: none"> 1. Conditions of use ✓ 2. Active ingredients ✓ 3. Route of administration ✓ 4. Dosage Form ✓ 5. Strength ✓ 	<p><input checked="" type="checkbox"/></p>
<p>Sec. V</p>	<p>Labeling</p> <ol style="list-style-type: none"> 1. 4 copies of draft (each strength and container) or 12 copies of FPL 2. 1 RLD label and 1 RLD container label 3. 1 side by side labeling comparison with all differences annotated and explained 	<p><input checked="" type="checkbox"/></p>
<p>Sec. VI</p>	<p>Bioavailability/Bioequivalence</p> <ol style="list-style-type: none"> 1. Financial Certification (Form FDA 3454) and Disclosure Statement (Form 3455) NO 2. Request for Waiver of In-Vivo Study(ies): YES 3. Formulation data same? (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) 4. Lot Numbers of Products used in BE Study(ies): 5. Study Type: (Continue with the appropriate study type box below) 	<p><input checked="" type="checkbox"/></p>
<p>Study Type</p>	<p>IN-VIVO PK STUDY(IES) (i.e., fasting/fed/sprinkle)</p> <ol style="list-style-type: none"> a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. Data Files (Computer Media) Submitted c. In-Vitro Dissolution 	<p><input type="checkbox"/></p>
<p>Study Type</p>	<p>IN-VIVO BE STUDY with CLINICAL ENDPOINTS</p> <ol style="list-style-type: none"> a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) d. Data Files (Computer Media) Submitted 	<p><input type="checkbox"/></p>
<p>Study Type</p>	<p>TRANSDERMAL DELIVERY SYSTEMS</p> <ol style="list-style-type: none"> a. <u>In-Vivo PK Study</u> <ol style="list-style-type: none"> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. Data Files (Computer Media) Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u> 	<p><input type="checkbox"/></p>

First Time
[generic Signal to]

Study Type	<p>NASALLY ADMINISTERED DRUG PRODUCTS</p> <p>a. <u>Solutions</u> (Q1/Q2 sameness):</p> <ol style="list-style-type: none"> 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) <p>b. <u>Suspensions</u> (Q1/Q2 sameness):</p> <ol style="list-style-type: none"> 1. In-Vivo PK Study <ol style="list-style-type: none"> a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. Data Files (Computer Media) Submitted 2. In-Vivo BE Study with Clinical EndPoints <ol style="list-style-type: none"> a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) d. Data Files (Computer Media) Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 	<input type="checkbox"/>
Study Type	<p>TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)</p> <p>a. Pilot Study (determination of ED50)</p> <p>b. Pivotal Study (study meets BE criteria 90%CI or 80-125)</p>	<input type="checkbox"/>
Sec. VII	<p>Components and Composition Statements <i>RL Labeling is Q & G.</i></p> <ol style="list-style-type: none"> 1. Unit composition and batch formulation ✓ 2. Inactive ingredients as appropriate ✓ 	<input checked="" type="checkbox"/>
Sec. VIII	<p>Raw Materials Controls</p> <ol style="list-style-type: none"> 1. Active Ingredients <ol style="list-style-type: none"> a. Addresses of bulk manufacturers b. Type II DMF authorization letters or synthesis c. COA(s) specifications and test results from drug substance mfr(s) d. Applicant certificate of analysis e. Testing specifications and data from drug product manufacturer(s) f. Spectra and chromatograms for reference standards and test samples g. CFN numbers 2. Inactive Ingredients <ol style="list-style-type: none"> a. Source of inactive ingredients identified b. Testing specifications (including identification and characterization) c. Suppliers' COA (specifications and test results) d. Applicant certificate of analysis 	<input checked="" type="checkbox"/>
Sec. IX	<p>Description of Manufacturing Facility</p> <ol style="list-style-type: none"> 1. Full Address(es) of the Facility(ies) 2. CGMP Certification YES 3. CFN numbers 	<input checked="" type="checkbox"/>

Sec. X	Outside Firms Including Contract Testing Laboratories 1. Full Address (b) (4) 2. Functions 3. CGMP Certification/GLP 4. CFN numbers	<input checked="" type="checkbox"/>
Sec. XI	Manufacturing and Processing Instructions 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) 3. If sterile product: (b) (4) 4. Filter validation (if aseptic fill) 5. Reprocessing Statement	<input type="checkbox"/>
Sec. XII	In-Process Controls 1. Copy of Executed Batch Record (Antibiotics/3 Batches if bulk product produced by fermentation) with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures). Batch Reconciliation and Label Reconciliation (b) (4) 2. In-process Controls - Specifications and data	<input checked="" type="checkbox"/>
Sec. XIII	Container 1. Summary of Container/Closure System (if new resin, provide data) 2. Components Specification and Test Data (Type III DMF References) 3. Packaging Configuration and Sizes (b) (4) 4. Container/Closure Testing 5. Source of supply and suppliers address	<input checked="" type="checkbox"/>
Sec. XIV	Controls for the Finished Dosage Form 1. Testing Specifications and Data 2. Certificate of Analysis for Finished Dosage Form	<input checked="" type="checkbox"/>
Sec. XV	Stability of Finished Dosage Form 1. Protocol submitted 2. Post Approval Commitments 3. Expiration Dating Period 4. Stability Data Submitted a. 3 month accelerated stability data b. Batch numbers on stability records the same as the test batch	<input checked="" type="checkbox"/>
Sec. XVI	Samples - Statement of Availability and Identification of: 1. Drug Substance 2. Finished Dosage Form 3. Same lot numbers	<input checked="" type="checkbox"/>
Sec. XVII	Environmental Impact Analysis Statement	<input checked="" type="checkbox"/>

Sec. XVIII	GDEA (Generic Drug Enforcement Act)/Other: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) 2. Debarment Certification (original signature) YES 3. List of Convictions statement (original signature)	<input checked="" type="checkbox"/>
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Reviewing CSO/CST Date: <i>Harvey Mealey</i>	Recommendation: <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE to RECEIVE
--	---

Supervisory Concurrence/Date: <i>[Signature]</i>	Date: <i>22-JAN-2003</i>
--	--------------------------

Duplicate copy sent to bio: (Hold if RF and send when acceptable)

Duplicate copy to HFD- for consult: Type:

ADDITIONAL COMMENTS REGARDING THE ANDA:

*Abbott w/d request for ped. exclusivity
NCE expired 9/23/02*

OGD Form Revised 11/30/2001
MSWord Template revised: 8/7/2002

*Formulation is Q₁/Q₂ based on approved
RLD labeling*



(b) (4)

**BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS
First Generic ANDA**

ANDA# 76-582 FIRM NAME Bedford Laboratories

DRUG NAME Fenoldopam Mesylate Injection USP 10mg/mL

DOSAGE FORM Injection 1mL & 2mL vials

Requested by: [Signature]
Chief, Regulatory Support Team, (HFD-615)

Summary of Findings by Division of Bioequivalence

- Study meets statutory requirements N/A
- Study does NOT meet statutory requirements
Reason:
- Waiver meets statutory requirements
- Waiver does NOT meet statutory requirements
Reason:

RECOMMENDATION: COMPLETE INCOMPLETE

Reviewed by:

Hocinhon Nguyen Date: 1-14-03
Reviewer

[Signature] Date: 1/15/2003
Team Leader

[Signature] Date: 1/15/03
Director, Division of Bioequivalence

76-582

Item Verified:	Yes	No	Required Amount	Amount Sent	Comments
Protocol					
Assay Methodology					
Procedure SOP					
Methods Validation					
Study Results Ln/Lin					
Adverse Events					
IRB Approval					
Dissolution Data					
Pre-screening of Patients					
Chromatograms					
Consent Forms					
Composition	✓				
Summary of Study					
Individual Data & Graphs, Linear & Ln					
PK/PD Data Disk (or Elec Subm)					
Randomization Schedule					
Protocol Deviations					
Clinical Site					
Analytical Site					
Study Investigators					
Medical Records					
Clinical Raw Data					
Test Article Inventory					

76-582

BIO Batch Size					
Assay of Active Content Drug					
Content Uniformity					
Date of Manufacture					
Exp. Date of RLD					
BioStudy Lot Numbers					
Statistics					
Summary results provided by the firm indicate studies pass BE criteria					
Waiver requests for other strengths / supporting data	✓				Waiver request ^{only} for 10mg/mL

Additional Comments regarding the ANDA:

RLD in ampules
Test in vials

Bartle, Margo L

From: Bartle, Margo L

Sent: Thursday, January 09, 2003 11:02 AM

To: Ames, Timothy W; Fang, Florence S; Holcombe Jr, Frank O; Patel, Rashmikant M; Sayeed, Vilayat A; Schwartz, Paul

Cc: Mueller, Albert J; Howard, Eda

Subject: first generic 76-582

FIRST GENERIC 76-582 FENOLDOPAM MESYLATE INJECTION USP, 10 MG/ML BEDFORD RECEIVED
12-19-2002

TEAM LEADER IS AL MUELLER

THANKS,

MARGO

1/9/03

Davis, Gregory S

From: Parise, Cecelia M
Sent: Wednesday, December 18, 2002 11:15 AM
To: Buehler, Gary J; West, Robert L; Rickman, William P; Ames, Timothy W; Davis, Gregory S; Hassall, Rita R; Hare, Donald B
Subject: FW: [REDACTED] (b) (4)
Importance: High

FYI,

[REDACTED] (b) (4)

Cec

-----Original Message-----

From: Carmouze, Grace N
Sent: Wednesday, December 18, 2002 10:37 AM
To: Jenkins, John K; Addy, Rosemary; Angel, James; Birenbaum, Debra L; Buckman, ShaAvhree; Ciampa, Aileen; Crescenzi, Terrie L; Cummins, Susan; Dettelbach, Kim; Dickinson, Elizabeth; Hirschfeld, Steven I; Hixon, Dena R; Holovac, Mary Ann; Hukle, Linda C; Iyasu, Solomon; Mathis, Lisa; Murphy, Dianne; Murphy, Shirley; Olnes, Susannah; Roberts, Rosemary; Rodriguez, William; Roman, Dragos; Sachs, Hari; Sheridan, Philip; Vaid, Sonal; Phucas, Kristin
Cc: Angel, James; Hukle, Linda C; West, Robert L; Parise, Cecelia M; Temple, Robert; Throckmorton, Douglas C; Robb, Melissa
Subject: RE: [REDACTED] (b) (4)
Importance: High

Dear Board Members,

[REDACTED] (b) (4)

Grace Carmouze
Regulatory Health Project Manager
Division of Pediatric Drug Development
Office of Counter-Terrorism and Pediatric Drug Development
Center for Drug Evaluation and Research
Telephone: 301/827-7737
Fax: 301/827-7727

-----Original Message-----

From: Jenkins, John K
Sent: Wednesday, December 11, 2002 4:59 PM
To: Carmouze, Grace N; Addy, Rosemary; Angel, James; Birenbaum, Debra L; Buckman, ShaAvhree; Ciampa, Aileen; Crescenzi, Terrie L; Cummins, Susan; Dettelbach, Kim; Dickinson, Elizabeth; Hirschfeld, Steven I; Hixon, Dena R; Holovac, Mary Ann; Hukle, Linda C; Iyasu, Solomon; Mathis, Lisa; Murphy, Dianne; Murphy, Shirley; Olnes, Susannah; Roberts, Rosemary; Rodriguez, William; Roman, Dragos; Sachs, Hari; Sheridan, Philip; Vaid, Sonal
Cc: Angel, James; Hukle, Linda C; West, Robert L; Parise, Cecelia M; Varki, Paul; Temple, Robert; Throckmorton, Douglas C
Subject: RE: [REDACTED] (b) (4)

Grace and others

[REDACTED] (b) (4)

John

-----Original Message-----

From: Carmouze, Grace N
Sent: Friday, December 06, 2002 6:34 PM
To: Addy, Rosemary; Angel, James; Birenbaum, Debra L; Buckman, ShaAvhree; Ciampa, Aileen; Crescenzi, Terrie L; Cummins, Susan; Dettelbach, Kim; Dickinson, Elizabeth; Hirschfeld, Steven I; Hixon, Dena R; Holovac, Mary Ann; Hukle, Linda C; Iyasu, Solomon; Jenkins, John K; Mathis, Lisa; Murphy, Dianne; Murphy, Shirley; Olnes, Susannah; Roberts, Rosemary; Rodriguez, William; Roman, Dragos; Sachs, Hari; Sheridan, Philip; Vaid, Sonal
Cc: Carmouze, Grace N; Angel, James; Hukle, Linda C; West, Robert L; Parise, Cecelia M; Varki, Paul
Subject: (b) (4)
Importance: High

Board Members,

(b) (4)

Attached is a memo from Dr. Avi Karkowsky summarizing the information submitted by the sponsor.

(b) (4)

Because there are no pending ANDAs for fenoldopam, we may need to go beyond our 90-day determination due date (12/19/02) to get this issue resolved.

I am waiting to hear back from the Division whether DSI will be notified of this situation.

Happy Friday!

<< (b) (4) >>

Grace Carmouze
 Regulatory Health Project Manager
 Division of Pediatric Drug Development
 Office of Counter-terrorism and Pediatric Drug Development
 Center for Drug Evaluation and Research
 Telephone: 301/827-7737
 Fax: 301/827-7727

ANDA 76-582

cc: DUP/Jacket

Division File

Field Copy

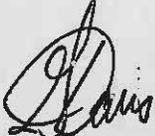
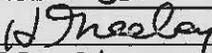
HFD-610/R.West

HFD-610/P.Rickman

HFD-92

HFD-615/M.Bennett

HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB  date 22-JAN-2003
HFD-615/HGreenber, CSO  date 1/22/2003
Word File V:/Firmsam/Bedford/Ltrs&rev/76582.ack
F/T EEH 01/22/03
ANDA Acknowledgment Letter!